



Ahfad University for Women

School of Health Sciences

MS Program in Nutrition and Dietetic

Advanced Human Nutrition: Clinical Reasoning

*A Practice-Oriented
Companion for the MS
Program in Nutrition and
Dietetics — AUW 2026*

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About this Supplement Reader

This supplement reader is designed for the **MS Program in Nutrition and Dietetics** at Ahfad University for Women. It serves as a clinical reasoning guide for advanced human nutrition, moving beyond basic biochemical memorization to focus on how dietitians respond to nutritional challenges. The reader emphasizes the "why" behind nutritional deficiencies, focusing on absorption barriers, increased metabolic demands, and medical conditions that deplete nutrient status. It is specifically built for clinical dietitians to bridge the gap between theory and the real-world clinical encounter.

How to Use this Supplement Reader?

The reader is structured around **Four Clinical Questions** intended to guide your practice throughout your career:

1. **What does this vitamin actually do in plain terms?** Provides the conceptual anchor and explains what breaks down when the nutrient is missing.
2. **What factors affect how much the body absorbs or uses?** Focuses on dietary counseling, including food preparation, drug interactions, and gut health.
3. **Who is genuinely at risk — and why?** Helps identify specific causes of risk for the individual patient rather than relying on population statistics.
4. **What does deficiency look like — and what is the dietitian's response?**
Connects biochemistry to clinical symptoms and actionable interventions.

Rather than just prescribing food, students should use this reader to find the underlying reason for a nutritional deficit.

Advanced Human Nutrition: Clinical Reasoning

A Practice-Oriented Companion for the MS Program in Nutrition and Dietetics

Professor Osama Awad Salih | Series No. 1 | AUW 2026

Contents

Module 1 — Micronutrients & Protective Elements

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

L
1

Fat-Soluble Vitamins: A · D · E · K

Absorption, Storage, Deficiency, Toxicity & Clinical Application

- ▶ Shared Properties — What Fat Solubility Means Clinically
- ▶ Vitamin A — Retinol, Retinal, Retinoic Acid & Beta-Carotene
- ▶ Vitamin D — The Sunshine Hormone: Synthesis, Activation & Non-Classical Roles
- ▶ Vitamin E — The Lipid-Phase Antioxidant & the Supplement Paradox
- ▶ Vitamin K — Coagulation, Bone Mineralization & Vascular Protection (MGP)
- ▶ Integrated Comparison: The Four Fat-Soluble Vitamins
- ▶ Clinical Case: Fatima — Coeliac Disease, Pregnancy & Fat-Soluble Vitamin Deficiency

L
2

Water-Soluble Vitamins: B-Complex · Vitamin C

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

- ▶ Part 1: The B Vitamins as Energy & Cell Builders
- ▶ B1 Thiamin | B2 Riboflavin | B3 Niacin | B5 Pantothenic Acid
- ▶ B6 Pyridoxine | B7 Biotin | B9 Folate | B12 Cobalamin
- ▶ Part 2: The One-Carbon Network — Folate, B12 & B6 Working Together
- ▶ Part 3: Vitamin C — Beyond Antioxidant
- ▶ Part 4: Integrating the Lecture — When Multiple B Vitamins Are Deficient

L
3

Minerals & Phytonutrients

Bioavailability, Whole-Food Principles & Health-Protective Mechanisms of Plant Compounds

- ▶ The Central Insight: Eating a Mineral Is Not the Same as Absorbing It
- ▶ Part 1: Major Minerals — Calcium | Magnesium | Phosphorus
- ▶ Part 2: Trace Minerals — Iron | Zinc | Iodine | Selenium
- ▶ Part 3: Phytonutrients — Polyphenols, Carotenoids, Organosulfur Compounds
- ▶ The Whole-Food Principle: Why Pattern Beats Supplement

Module 2 — Body Regulation & Composition

Internal Balance & Physical Assessment

L 1 **Fluids & Electrolytes**

Body Fluid Compartments, Electrolyte Physiology, pH Balance & Clinical Disorders

- ▶ Part 1: Body Water — Compartments, Forces & Osmolality
- ▶ Part 2: The Water Regulation System — ADH, Thirst & SIADH
- ▶ Part 3: Sodium — Hyponatraemia, Hypernatraemia & Correction Rates
- ▶ Part 4: Potassium — Membrane Potential, Hypokalaemia & Hyperkalaemia
- ▶ Part 5: Chloride, Bicarbonate & the Four Acid-Base Disturbances
- ▶ Part 6: Clinical Application — Refeeding Syndrome | GI Losses | Parenteral Nutrition
- ▶ Clinical Case: Amira — Anorexia Nervosa, Collapse & Electrolyte Emergency

L 2 **Body Composition**

Models, Lifespan Changes, Measurement Techniques & Clinical Assessment

- ▶ Part 1: Body Composition Models — 2C, 3C & 4C Frameworks
- ▶ Part 2: Assessment Methods — Anthropometry | BIA | DEXA | ADP | CT/MRI/Ultrasound
- ▶ Part 3: Adiposity — VAT, SAT, Ectopic Fat & the Adipokine Profile
- ▶ Part 4: Sarcopenia — EWGSOP2 Criteria, Mechanisms & Nutritional Management
- ▶ Part 5: BMI — Legitimate Uses & Systematic Limitations
- ▶ Part 6: Special Populations — Malnutrition | Athletes | Older Adults
- ▶ Clinical Case: Three Women, One BMI — Body Composition Phenotypes

Module 3 — Nutritional Assessment & Specialized Needs

Evaluating Intake & Requirements Across Populations

L 1 **Energy Balance & Metabolism**

Energy Expenditure, Macronutrient Metabolism, Hunger Regulation & Clinical Energy Prescription

- ▶ Part 1: Total Energy Expenditure — BMR, TEF, AEE & NEAT
- ▶ Part 2: Macronutrient Metabolism — Substrate Hierarchy, RQ & the Fuel Hierarchy
- ▶ Part 3: Hunger, Satiety & Neuroendocrine Regulation — Leptin, Ghrelin, GLP-1, PYY, CCK
- ▶ Part 4: Adaptive Thermogenesis & Metabolic Adaptation — Why Weight Loss Slows
- ▶ Part 5: Clinical Energy Prescription — Critical Illness | Obesity | Cachexia | Pregnancy
- ▶ Clinical Case: Khalid — Office-Based Weight Gain, Plateau & Substrate Metabolism

L 2 **Nutritional Assessment**

From Screening to Diagnosis — Tools, Biomarkers, Dietary Methods & the ADIME Framework

- ▶ Part 1: Screening vs. Assessment — Two Different Questions
- ▶ Part 2: Validated Screening Tools — MUST | NRS-2002 | MNA | STAMP | PG-SGA
- ▶ Part 3: The ABCDE Assessment Framework — Anthropometric | Biochemical | Clinical | Dietary | Environmental
- ▶ Part 4: Diagnosing Malnutrition — The GLIM Criteria
- ▶ Part 5: The Nutrition Care Process — ADIME Documentation & the PES Statement
- ▶ Part 6: Population-Level Assessment — SMART Surveys, GAM, SAM & Sudan Context
- ▶ Clinical Case: Hana — Elderly Malnutrition, Social Isolation & ADIME Documentation

Module 4 — Oxidative Stress, Phytochemicals & Functional Foods

A 3-Lecture Graduate Series: Free Radicals & Antioxidants • Phytochemicals • Fruits & Vegetables

L

1

Free Radicals & Antioxidant Defense

Biochemical Mechanisms, Chronic Disease Pathways & Therapeutic Strategies

- ▶ Part 1: What Are Free Radicals and Why Do They Form?
- ▶ Part 2: How Free Radicals Damage the Body — Lipids, Proteins, DNA & AGEs
- ▶ Part 3: The Antioxidant Defense System — Enzymatic, Glutathione & Nrf2 Pathway
- ▶ Part 4: Oxidative Stress in Chronic Disease — CVD | Cancer | Type 2 Diabetes
- ▶ Part 5: Why Antioxidant Supplements Fail While Dietary Patterns Succeed
- ▶ Part 6: Practical Guidance — Dietary Strategies & Lifestyle Factors
- ▶ Clinical Case: Ahmed — Diabetic Teacher, Khartoum & Oxidative Stress Management

L

2

Phytochemicals: Sources & Benefits

Classification, Bioavailability, Mechanisms of Action & Chronic Disease Evidence

- ▶ Part 1: How Phytochemicals Work — Nrf2, NF-κB, AMPK & Gut Microbiome
- ▶ Part 2: The Major Phytochemical Families — Flavonoids | Phenolic Acids | Lignans | Glucosinolates | Allium | Carotenoids | Phytosterols | Curcumin | Berberine
- ▶ Part 3: Bioavailability — The Four Determinants & the Microbiome as Transformer
- ▶ Part 4: The Evidence Hierarchy — Strong | Moderate | Preliminary | Insufficient
- ▶ Clinical Case: Fatima — Nurse, Pre-Diabetes, Hypercholesterolaemia & Phytochemical Strategy

L

3

Fruits & Vegetables: Micronutrient Powerhouses

Nutritional Composition, Bioavailability, Public Health Evidence & Counselling Strategies

- ▶ Part 1: The Public Health Case — Global & Sudanese F&V Gap
- ▶ Part 2: Nutritional Profiles by Group — 8 F&V Groups with Sudanese Context
- ▶ Part 3: The Cooking Question — How Preparation Affects Nutrient Delivery
- ▶ Part 4: Disease Connections — CVD | Cancer | Type 2 Diabetes
- ▶ Part 5: Counselling in Practice — Barriers, Colour Framework & Special Populations
- ▶ Clinical Case: Nadia — Port Sudan, Hypertension, Pre-Diabetes & Postpartum Anaemia

Each lecture follows the Clinical Reasoning Approach — structured around four core questions: What does this nutrient do? What factors affect absorption and use? Who is genuinely at risk and why? What does deficiency look like and what is the dietitian's response? Every lecture includes: WHY / PRACTICE / CAUTION / CONNECT / EVIDENCE note blocks — factor and risk tables — a named Sudanese clinical case scenario — and critical thinking questions for graduate-level reflection.

Module 1 — Micronutrients & Protective Elements

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

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Fat-Soluble Vitamins: A · D · E · K

Absorption, Storage, Deficiency, Toxicity & Clinical Application

- ▶ Shared Properties — What Fat Solubility Means Clinically
- ▶ Vitamin A — Retinol, Retinal, Retinoic Acid & Beta-Carotene
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Fat-Soluble Vitamins

Vitamins A, D, E & K — Absorption, Storage, Deficiency, Toxicity & Clinical Application

Focus: What makes fat-soluble vitamins clinically unique — from silent deficiency to life-threatening toxicity

The Fat-Soluble Vitamins: What Makes Them Different

Vitamins A, D, E, and K share a defining property: they are soluble in fat and fat solvents, not in water. This single biochemical characteristic generates a cascade of clinically important consequences that distinguish them from every water-soluble vitamin in the series. Understanding the shared properties of fat solubility — and the individual clinical profiles of each vitamin — is essential for managing the patients most likely to have problems with them.

Shared Property	Clinical Consequence	Practical Implication
Absorbed with dietary fat via chylomicrons	Any condition that impairs fat absorption impairs all four vitamins simultaneously: cystic fibrosis, coeliac disease, Crohn's disease, short bowel syndrome, cholestatic liver disease, pancreatic exocrine insufficiency, post-bariatric surgery (especially bypass procedures)	Always assess fat-soluble vitamin status in patients with fat malabsorption. A patient with untreated coeliac disease may be deficient in A, D, E, and K simultaneously.
Stored in liver and adipose tissue	Unlike water-soluble vitamins (excreted in urine when excess), fat-soluble vitamins accumulate. Toxicity is possible — and for vitamins A and D, clinically significant toxicity is well documented.	Supplementation must be dosed carefully. Fat stores provide a buffer against short-term dietary inadequacy — deficiency develops more slowly than for water-soluble vitamins but is harder to reverse once established.
Require bile salts for micellar solubilisation	Cholestasis (obstructive jaundice, primary biliary cholangitis, biliary atresia in infants) impairs micelle formation and dramatically reduces fat-soluble vitamin absorption even when dietary intake is adequate.	Check fat-soluble vitamin status in any patient with cholestatic liver disease or biliary obstruction. Water-miscible (emulsified) formulations of fat-soluble vitamins bypass this problem and are used in cholestasis.
Transport in lipoproteins	Depend on lipoprotein status for tissue delivery; abetalipoproteinaemia (inability to make apoB-containing lipoproteins) causes profound fat-soluble vitamin deficiency even with adequate dietary intake.	In rare lipid transport disorders, standard dietary correction is ineffective. Massive supplementation with water-miscible forms or direct tissue-targeted delivery may be required.

Interact with each other	Vitamins A and K share liver metabolism pathways; vitamin E protects vitamin A from oxidation; very high vitamin E supplementation can antagonize vitamin K activity; vitamin D regulates genes involved in vitamin A signaling.	Supplementing one fat-soluble vitamin at high doses can affect others. Monitoring all four is important in patients on complex supplementation regimens.
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Learning Outcomes — By the end of this lecture, students will be able to:

- Explain the absorption, transport, storage, and metabolism of each fat-soluble vitamin and identify the conditions that impair these processes
- Describe the key biochemical functions of vitamins A, D, E, and K and connect each function to a specific clinical deficiency syndrome
- Identify the at-risk populations for each fat-soluble vitamin deficiency — globally and in the Sudanese/East African context
- Explain the clinical features, biochemical assessment, and treatment of deficiency for each vitamin
- Describe the toxicity syndromes for vitamins A and D — recognize the clinical presentations and management principles
- Apply knowledge of drug–nutrient interactions affecting fat-soluble vitamins to clinical practice (warfarin/vitamin K; cholestyramine; orlistat; anticonvulsants; glucocorticoids)
- Counsel patients on appropriate supplementation across clinical contexts: pregnancy, malabsorption, liver disease, exclusive breastfeeding, dark-skinned populations in low-sunlight environments

VITAMIN A — Retinol, Retinal, Retinoic Acid & Beta-Carotene

Vitamin A is not a single compound but a family of structurally related molecules — collectively called retinoids — along with provitamin A carotenoids (primarily beta-carotene) that the body can convert to active retinol. Understanding the difference between preformed vitamin A (retinol) and provitamin A (beta-carotene) is clinically critical because their bioavailability, toxicity risk, and dietary sources are completely different.

Vitamin A

Retinoid Forms, Provitamin A & the Vision-Immunity-Epithelium Triad

Forms, Sources and Conversion

Form	Source	Conversion to Active Vitamin A	Toxicity Risk
Retinol (preformed vitamin A)	Animal sources: liver (highest — beef liver 9,442 µg RAE/100g), oily fish	Already active — no conversion needed; absorbed as retinyl esters in chylomicrons; stored in	HIGH — absorbed efficiently regardless of

	(halibut liver oil), egg yolk, full-fat dairy, fortified foods	hepatic stellate cells (Ito cells) as retinyl palmitate	body status; liver stores accumulate; toxicity (hypervitaminosis A) occurs with chronic high intake. Teratogenic at high doses in pregnancy.
Beta-carotene (provitamin A)	Plant sources: sweet potato, carrots, pumpkin, dark leafy greens (molokhia, spinach, kale), mango, papaya, red palm oil	Cleaved by beta-carotene 15,15'-dioxygenase in enterocytes to 2 molecules of retinal → retinol. Conversion ratio: 12 µg dietary beta-carotene = 1 µg RAE (retinol activity equivalent). Conversion is down-regulated when retinol stores are adequate — built-in safety mechanism.	SAFE — excess beta-carotene causes carotenoderma (yellow-orange skin coloration) but NOT hypervitaminosis A. The down-regulation of conversion prevents toxicity from dietary plant sources.
Other carotenoids (α-carotene, β-cryptoxanthin)	Orange/yellow fruits and vegetables	Lower provitamin A activity than beta-carotene (24 µg = 1 µg RAE for α-carotene and β-cryptoxanthin)	Safe — same protective down-regulation applies
Retinoic acid (all-trans and 9-cis)	Formed from retinol by sequential oxidation in tissues	The primary transcriptionally active form; regulates gene expression via RAR and RXR nuclear receptors; cannot be converted back to retinol or stored	Not present in significant amounts in food; pharmacological retinoids (isotretinoin, tretinoin, acitretin) are synthetic retinoic acid derivatives used in dermatology and oncology — carry high teratogenic risk

Functions of Vitamin A — The Clinical Triad

Function	Mechanism	Deficiency Consequence	Clinical Significance
VISION (Retinal function)	11-cis-retinal is the chromophore of rhodopsin (rod photopigment) and cone opsins. Light isomerizes 11-cis to all-trans-retinal → triggers	Night blindness (nyctalopia): earliest clinical sign of VAD. Severe deficiency → xerophthalmia	Night blindness in children is a reportable public health indicator in many countries.

	phototransduction cascade. Rhodopsin regeneration requires retinol from RPE cells.	progression (Bitot's spots → corneal ulceration → keratomalacia → permanent blindness)	Bitot's spots (foamy, white, cheese-like deposits on conjunctiva) are pathognomonic for VAD. Vitamin A deficiency is the leading cause of preventable childhood blindness globally.
EPITHELIAL INTEGRITY (Retinoic acid function)	Retinoic acid (RAR/RXR signaling) regulates differentiation of epithelial cells. Maintains mucus-secreting goblet cells in respiratory, GI, and urinary tract epithelia. Promotes keratinocyte differentiation; prevents squamous metaplasia.	Squamous metaplasia: mucus-secreting epithelium replaced by non-secreting squamous epithelium — in respiratory tract, GI tract, urinary tract, conjunctiva. Reduced mucosal barrier → increased susceptibility to infection. Follicular hyperkeratosis (rough, bumpy skin from keratin plugs in hair follicles) is an early skin sign.	Explains why VAD causes increased severity of infections (measles, diarrhoea, respiratory infection). Reduced mucus layer removes the first line of pathogen defense. VAD-infected children have 2–3× higher measles mortality — the basis for vitamin A supplementation at measles diagnosis.
IMMUNE FUNCTION (Retinoic acid function)	Retinoic acid promotes differentiation of T-regulatory cells and IgA-producing plasma cells in gut-associated lymphoid tissue (GALT). Maintains innate immunity at mucosal surfaces. Regulates NK cell and macrophage function.	Impaired mucosal immunity: reduced secretory IgA, reduced T-reg function → increased severity and duration of diarrhoeal and respiratory infections. VAD children have higher all-cause and infection-specific mortality.	The immune-vitamin A link is so strong that WHO recommends two high-dose vitamin A supplements (100,000–200,000 IU) to all children diagnosed with measles in high-VAD settings — regardless of apparent vitamin A status — because measles itself depletes vitamin A stores.
GENE REGULATION (Retinoic acid / RXR heterodimerization)	RXR (Retinoid X Receptor) heterodimerizes with multiple nuclear receptors: PPAR γ (fat metabolism), LXR (cholesterol), FXR (bile acids), thyroid receptor, vitamin D receptor. Retinoic acid therefore modulates fat, cholesterol, bile acid, and thyroid hormone signaling.	Complex pleiotropic effects of severe deficiency on metabolism; exacerbated by interactions with other fat-soluble vitamins (especially vitamin D whose receptor requires RXR as a dimerization partner)	Explains why chronic VAD affects multiple metabolic pathways beyond vision and immunity. Also explains why pharmacological retinoids have effects on lipid metabolism (hypertriglyceridaemia is a side effect of isotretinoin).
REPRODUCTION & DEVELOPMENT (Retinoic acid)	Essential for spermatogenesis; embryonic development (limb patterning, organogenesis, CNS	Infertility; spontaneous abortion; congenital malformations (craniofacial, cardiac,	Both too little and too much vitamin A during pregnancy is dangerous.

	development); placental function.	CNS) — caused by both deficiency AND excess (teratogenicity).	Deficiency: risk of maternal night blindness (common in South Asia and Sub-Saharan Africa), adverse birth outcomes. Excess (supplements or liver): risk of teratogenesis.
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Deficiency: Assessment, At-Risk Groups & Treatment

Aspect	Detail
Global burden	Vitamin A deficiency (VAD) affects approximately 190 million children under 5 and 19 million pregnant women globally. Sub-Saharan Africa and South/Southeast Asia account for >90% of burden. VAD is the leading cause of preventable childhood blindness (250,000–500,000 children/year) and contributes substantially to child mortality from infectious disease.
Clinical staging (WHO xerophthalmia classification)	XN: Night blindness (earliest sign). X1A: Conjunctival xerosis (dry, dull conjunctiva). X1B: Bitot's spots. X2: Corneal xerosis. X3A: Corneal ulceration (<1/3 cornea). X3B: Corneal ulceration (≥1/3 cornea). XS: Corneal scarring. XF: Xerophthalmic fundus. Stages X2 onwards are sight-threatening emergencies.
Biochemical assessment	Serum retinol: normal ≥0.7 µmol/L; marginal deficiency <0.7 µmol/L; severe <0.35 µmol/L. Limitations: serum retinol is a poor indicator of liver stores (homeostatic regulation maintains serum level until liver stores are nearly depleted); falls with infection (acute-phase response). Modified Relative Dose Response (MRDR) test is more sensitive for liver store assessment but requires two blood draws.
At-risk groups	Children 6 months–5 years in VAD-endemic areas (Sub-Saharan Africa, South Asia); Pregnant and lactating women; Exclusively breastfed infants of VAD-deficient mothers (breast milk retinol reflects maternal status); Fat malabsorption conditions (coeliac, CF, Crohn's, post-bariatric surgery); Chronic liver disease (impaired storage and retinol-binding protein synthesis); Strict vegans eating inadequate provitamin A foods.
Sudan-specific context	VAD is a significant public health problem in Sudan, particularly in rural areas, children under 5, and pregnant women. The National Micronutrient Survey has documented VAD prevalence exceeding 30% in children in some states. Red palm oil (widely available in parts of Sudan and adjacent East Africa) is an exceptionally rich provitamin A source (540 µg RAE/100g) and is used in some fortification programs. Molokhia (jute mallow) and pumpkin are important local provitamin A sources that should be emphasized in dietary counselling.
Treatment	Mild-moderate deficiency (dietary + low-dose supplement): food-based approach + 10,000–25,000 IU/day orally. Severe VAD / xerophthalmia (WHO protocol): Day 1: 200,000 IU orally (100,000 IU if <12 months or <8 kg); Day 2: 200,000 IU; At discharge or 4 weeks later: 200,000 IU. Measles in high-VAD settings: same high-dose protocol. Water-miscible formulations for fat malabsorption.

CAUTION

Vitamin A toxicity — Hypervitaminosis A: Acute toxicity (single dose >150,000 µg RAE in adults): nausea, vomiting, headache, dizziness, blurred vision, bulging fontanelle in infants, desquamation. Chronic toxicity (prolonged intake >10,000 IU/day in adults, much lower in children): hepatotoxicity (fibrosis, cirrhosis), bone pain and fractures (paradoxically increases fracture risk by inhibiting osteoblasts), alopecia, dry/peeling skin, hyperlipidaemia, intracranial hypertension (pseudotumour cerebri). Teratogenicity: intake >10,000 IU/day preformed vitamin A in the first trimester is associated with craniofacial, cardiac, and CNS malformations. Pregnant women must NOT consume liver more than once a week and must avoid high-dose retinol supplements (standard prenatal vitamins are safe). Beta-carotene supplements do NOT cause teratogenicity.

CONNECT

Isotretinoin (13-cis-retinoic acid) and pregnancy: Isotretinoin is a potent synthetic retinoid used for severe acne. It is one of the most teratogenic drugs known — a single course taken during the first trimester causes major congenital abnormalities in >20% of exposed pregnancies. Women prescribed isotretinoin must use two forms of contraception simultaneously and have negative pregnancy tests before, during, and after treatment. Dietitians in settings where isotretinoin is prescribed should be aware of the strict dietary vitamin A restriction that accompanies treatment and the absolute contraindication to pregnancy.

VITAMIN D — The Sunshine Hormone

Vitamin D occupies a unique position among vitamins: it is primarily synthesized in the skin by ultraviolet B radiation acting on 7-dehydrocholesterol — making it technically a hormone precursor rather than a dietary vitamin in the traditional sense. Dietary sources alone are rarely sufficient to maintain optimal status without sun exposure. Yet global vitamin D deficiency is pandemic, affecting an estimated 1 billion people including populations in sun-rich regions like Sudan, where cultural and religious dress practices, skin pigmentation, and indoor lifestyles limit cutaneous synthesis.

Vitamin D

Synthesis, Activation, the Calcium-Bone Axis & the Expanding Evidence for Non-Classical Roles

Synthesis, Activation and the Two-Step Hydroxylation Pathway

Step	Location	Product	Regulatory Control
Cutaneous synthesis	Skin (keratinocytes): UVB (290–315 nm) converts 7-dehydrocholesterol → pre-vitamin D3 → thermal isomerization → cholecalciferol (vitamin D3)	Cholecalciferol (D3) — inactive	Limited by: melanin (skin pigmentation absorbs UVB — dark-skinned individuals need 3–6× more sun exposure); sunscreen (SPF 15 reduces synthesis by 95%); latitude (inadequate UVB at >35°N or >35°S for several

			months/year); clothing coverage; glass (blocks UVB); age (elderly skin has reduced 7-dehydrocholesterol → reduced synthesis capacity)
Dietary intake	GI absorption: vitamin D2 (ergocalciferol, from fungi/yeast/fortified foods) and D3 (cholecalciferol, from animal sources) absorbed with fat in chylomicrons	Cholecalciferol (D3) or ergocalciferol (D2) — inactive	D3 is ~1.7–3× more potent than D2 at raising 25(OH)D levels; both are biologically active after hydroxylation. Food sources of D3: oily fish (salmon: 400–600 IU/100g; sardines: 300 IU); egg yolk; fortified dairy and plant milks.
First hydroxylation	Liver (CYP2R1/CYP27A1): 25-hydroxylation of D3/D2	25-hydroxyvitamin D [25(OH)D] — the storage form and clinical measurement; long half-life (~3 weeks); reflects total vitamin D status	Minimally regulated — this step is largely substrate-dependent, not tightly controlled. Thus serum 25(OH)D rises linearly with increasing vitamin D input (dietary + cutaneous) until very high levels.
Second hydroxylation	Kidney (CYP27B1 / 1 α -hydroxylase): converts 25(OH)D → 1,25-dihydroxyvitamin D	1,25-dihydroxyvitamin D [1,25(OH) ₂ D] — calcitriol; the biologically active hormone; acts on vitamin D receptor (VDR)	Tightly regulated: stimulated by PTH (rising when Ca ²⁺ falls); suppressed by FGF-23 (fibroblast growth factor 23 from bone, which rises with high phosphate); suppressed by elevated calcium and calcitriol itself (negative feedback). In CKD: this step fails → secondary hyperparathyroidism, renal osteodystrophy.
Extra-renal 1 α -hydroxylation	Macrophages, dendritic cells, keratinocytes, placenta, breast, prostate, colon	Local 1,25(OH) ₂ D for paracrine/autocrine effects	Not regulated by PTH; driven by substrate (25(OH)D) availability and local immune signals (IFN- γ , lipopolysaccharide). Explains why adequate 25(OH)D is needed for immune function — macrophages convert

			it locally to calcitriol for antimicrobial peptide (defensin, cathelicidin) synthesis.
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Functions: Classical Calcium-Bone Axis

Target Organ	VDR-Mediated Action	Consequence of Deficiency
Small intestine (duodenum)	Calcitriol stimulates synthesis of calbindin (calcium-binding protein), TRPV6 (apical calcium channel), and PMCA1b (basolateral calcium pump) → active calcium absorption increases 2–3 fold	Without calcitriol: passive calcium absorption only (15–20% of intake vs 30–40% with adequate vitamin D); insufficient calcium absorbed to maintain serum calcium
Kidney (distal tubule)	Stimulates calcium and phosphate reabsorption via TRPV5 and sodium-phosphate cotransporters	Increased urinary calcium and phosphate losses; contributes to negative calcium balance
Bone	Directly: VDR on osteoblasts promotes mineralization and bone remodeling. Indirectly: by maintaining calcium and phosphate levels adequate for hydroxyapatite crystal formation	Impaired bone mineralization: rickets (children — unmineralized growth plate cartilage); osteomalacia (adults — unmineralized osteoid seams on existing bone). Distinct from osteoporosis (reduced bone density but normal mineralization).
Parathyroid gland	Calcitriol suppresses PTH gene transcription → reduces PTH secretion when calcium is adequate	Vitamin D deficiency → secondary hyperparathyroidism (PTH chronically elevated to maintain serum calcium) → bone resorption accelerated → bone loss; renal calcium reabsorption; renal phosphate wasting

Non-Classical Functions — The Expanding Evidence

The VDR is expressed in virtually every tissue of the human body — including immune cells, muscle, brain, pancreas, cardiovascular tissue, and colon. This near-ubiquitous expression suggests that calcitriol has functions far beyond calcium homeostasis. The evidence for these non-classical roles varies from strong (immune function, muscle function) to promising but not yet conclusive (cardiovascular, cancer, metabolic disease).

Non-Classical Role	Mechanism	Evidence Level	Clinical Application
Immune regulation	VDR in macrophages, dendritic cells, T and B cells. Extra-renal calcitriol synthesis enables local immune modulation. Induces antimicrobial peptides (cathelicidin LL-37, beta-defensin 2) that are directly	STRONG for innate immunity (TB risk inversely associated with vitamin D status in multiple studies; RCTs show vitamin D supplementation reduces TB	Check vitamin D status in patients with recurrent infections, TB, or autoimmune disease. Supplement deficient patients. In

	microbicidal against TB, influenza, COVID-19, and other pathogens. Suppresses pro-inflammatory Th1/Th17 cytokines; promotes regulatory T-cell differentiation.	progression risk by 40% in deficient patients). MODERATE for respiratory tract infection prevention (meta-analysis of 25 RCTs, n>11,000: supplementation reduced acute respiratory tract infections by 12–42% in deficient individuals).	Sudan: TB is prevalent; vitamin D deficiency is common; both respond to adequate supplementation.
Muscle function	VDR in muscle cells; calcitriol promotes protein synthesis, calcium signaling in muscle, and Type II fast-twitch fibre maintenance. Low vitamin D associated with impaired muscle strength, balance, and fall risk.	STRONG for fall and fracture prevention in older adults with deficiency: meta-analysis of RCTs shows 700–1000 IU/day reduces fall risk by 19% in vitamin D-deficient older adults (Bischoff-Ferrari et al., BMJ 2009). Effect is specific to deficiency correction — supplementing replete individuals shows no benefit.	Screen older adults for vitamin D deficiency as part of falls risk assessment. Target 25(OH)D $\geq$ 75 nmol/L (30 ng/mL) in older adults for optimal muscle and bone outcomes.
Insulin secretion and sensitivity	VDR in pancreatic β -cells; calcitriol promotes insulin gene transcription and calcium-stimulated insulin secretion. Also modulates insulin receptor signaling in peripheral tissues.	MODERATE: large observational studies show inverse association between vitamin D status and T2DM incidence. RCTs (VITAL-D, D-HEALTH) show modest benefit for glucose metabolism in deficient individuals but no major T2DM prevention effect in replete populations.	In newly diagnosed T2DM or pre-diabetes: check and correct vitamin D deficiency. Do not overstate — supplementing replete patients does not significantly improve glycaemic control.
Cardiovascular health	VDR in cardiomyocytes and vascular smooth muscle; calcitriol modulates RAAS (suppresses renin gene transcription); anti-inflammatory effects reduce atherosclerosis risk.	MODERATE observational; weaker RCT evidence. VITAL trial (n=25,871): vitamin D 2000 IU/day did not reduce major cardiovascular events overall, but reduced cardiovascular mortality in Black participants and those with low baseline levels.	Correct deficiency for general health benefit. Do not use vitamin D supplementation as primary cardiovascular preventive therapy in replete individuals.
Cancer	VDR promotes cell differentiation, inhibits	MODERATE observational; mixed	Maintain adequate vitamin D status as

	proliferation, promotes apoptosis in multiple cancer cell lines. Inverse observational association with colorectal, breast, and prostate cancer.	RCT evidence. VITAL trial: no significant reduction in total cancer incidence with D3 2000 IU/day, but significant reduction in cancer mortality (17% lower) after 2+ years — suggesting vitamin D may slow cancer progression rather than prevent initiation.	part of overall cancer risk reduction strategy. Do not recommend high-dose supplementation as cancer treatment.
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Deficiency: Status Assessment, At-Risk Groups & Treatment

Aspect	Detail
25(OH)D thresholds (widely used)	Deficient: <30 nmol/L (<12 ng/mL) — rickets/osteomalacia risk; Insufficient: 30–49 nmol/L (12–19 ng/mL) — suboptimal for bone and muscle; Sufficient: 50–74 nmol/L (20–29 ng/mL) — adequate for most; Optimal: ≥75 nmol/L (≥30 ng/mL) — for muscle, immune, and fall prevention benefit; Excessive: >250 nmol/L (>100 ng/mL) — risk of toxicity; Toxic: >375 nmol/L (>150 ng/mL)
Clinical deficiency syndromes	Rickets (children): widening of wrist and ankle growth plates; rachitic rosary (beaded costochondral junctions); bowing of weight-bearing long bones; delayed fontanelle closure; hypocalcaemic tetany; dental enamel defects. Osteomalacia (adults): bone pain (especially lower back, hips, legs); tenderness on bone palpation; proximal muscle weakness; Looser zones (pseudofractures) on X-ray. Both: secondary hyperparathyroidism; elevated alkaline phosphatase; low/normal calcium; low phosphate.
The Sudan/tropical paradox	Sudan has abundant sunlight year-round — yet vitamin D deficiency is common. The explanation: (1) Cultural and religious dress practices (hijab, niqab, jilbab) that cover most of the skin dramatically reduce cutaneous synthesis. (2) Skin pigmentation (higher melanin content) requires 3–6× more sun exposure for equivalent synthesis. (3) Avoidance of midday sun (when UVB is highest) due to extreme heat. (4) Very few vitamin D-rich foods in the local diet. This combination makes vitamin D deficiency common even in equatorial populations — a critical counselling point for dietitians working in Sudan, East Africa, and the Middle East.
At-risk groups	Exclusively breastfed infants (breast milk contains very little vitamin D — 10–80 IU/L; WHO recommends 400 IU/day supplement for all breastfed infants); Elderly (reduced skin synthesis, reduced outdoor activity, reduced renal activation); Pregnant and lactating women; Veiled women and people with minimal sun exposure; People with dark skin pigmentation in low-sunlight environments; Fat malabsorption conditions; Obesity (vitamin D sequestered in adipose tissue; diluted by large body volume); CKD (impaired renal 1α-hydroxylation); Anticonvulsant medications (CYP450 induction accelerates D catabolism).
Treatment guidelines	Deficiency correction: 4,000–6,000 IU/day D3 for 8–12 weeks, then 1,500–2,000 IU/day maintenance; OR 50,000 IU/week D3 for 8 weeks (prescription strength). Maintenance for at-risk groups: 1,000–2,000 IU/day D3. Breastfed infants: 400 IU/day from birth. Older adults (≥65 years): 800–1,000 IU/day with calcium 1,000–1,200 mg/day for bone and fall prevention. In CKD: use 1,25(OH) ₂ D (calcitriol) directly — standard vitamin D supplements are ineffective because renal 1α-hydroxylation is impaired.

CAUTION

Vitamin D toxicity — Hypervitaminosis D: Not caused by sun exposure (skin synthesis is self-limiting). Caused by excessive supplementation — typically >10,000 IU/day for extended periods, or high-dose bolus protocols. Mechanism: hypercalcaemia from excessive intestinal calcium absorption and bone resorption. Symptoms: nausea, vomiting, weakness, confusion, polyuria, polydipsia, nephrocalcinosis (calcium deposits in kidney), renal failure, arrhythmias. Serum 25(OH)D >375 nmol/L (>150 ng/mL) is considered toxic. Treat with immediate cessation of supplement, hydration, and glucocorticoids (reduce intestinal calcium absorption). Annual high-dose bolus supplementation (300,000–500,000 IU single dose) has been associated with paradoxically increased falls risk in some RCTs — mechanism unclear; avoid bolus dosing in favour of regular daily supplementation.

VITAMIN E — The Lipid-Phase Antioxidant

Vitamin E is a collective term for eight naturally occurring compounds — four tocopherols (α , β , γ , δ) and four tocotrienols (α , β , γ , δ). Of these, α -tocopherol is the form preferentially retained by the human body through selective hepatic secretion via the α -tocopherol transfer protein (α -TTP), and it is the form with the highest biological antioxidant activity in membranes.

Vitamin E

α -Tocopherol, Membrane Antioxidant Defence & the Fat-Soluble Antioxidant Network

Functions

Function	Mechanism	Clinical Relevance
Lipid peroxidation chain-breaking antioxidant (primary function)	Embedded in cell membranes and lipoprotein particles; donates hydrogen to lipid peroxyl radicals ($\text{LOO}\cdot$) $\rightarrow$ forming lipid hydroperoxide (LOOH , relatively stable) and tocopheroxyl radical ($\text{TO}\cdot$). $\text{TO}\cdot$ is regenerated to α -tocopherol by vitamin C (aqueous phase), glutathione, and NADPH via the antioxidant network. This chain-breaking action prevents one lipid peroxidation event from propagating through an entire membrane.	Protects: polyunsaturated fatty acids in cell membranes (especially neuronal and red blood cell membranes) from oxidative destruction; LDL from oxidation (oxidized LDL is the initiating step in atherosclerotic plaque formation); vitamin A from oxidative degradation in the gut. Low vitamin E $\rightarrow$ accelerated PUFA peroxidation $\rightarrow$ membrane dysfunction.
Immune modulation	Enhances T-lymphocyte proliferation; inhibits cyclooxygenase-2 (COX-2) and reduces prostaglandin E2 production; modulates cytokine production	Adequate vitamin E supports immune function, particularly in elderly (who have lower plasma vitamin E and impaired immunity). Supplementation (200–400 IU/day) in elderly improved delayed hypersensitivity response and antibody response to hepatitis B vaccine in RCTs.
Anti-platelet / vasodilatory effects	Inhibits protein kinase C in platelets $\rightarrow$ reduces platelet	Modest antiplatelet effect at high doses. Clinically significant drug interaction:

	aggregation; inhibits COX in vascular endothelium; regulates VCAM-1 expression (adhesion molecule for monocytes) in endothelial cells	vitamin E $\geq 1,000$ mg/day can potentiate warfarin anticoagulation by inhibiting vitamin K-dependent clotting factor synthesis. Monitor INR in patients taking both.
Gene regulation	Acts as a ligand for PPARs (Peroxisome proliferator-activated receptors); regulates genes involved in lipid metabolism, inflammation, and cell cycle	Secondary to antioxidant function in most clinical contexts; emerging evidence for tocotrienols in gene regulation

Deficiency

Vitamin E deficiency from inadequate dietary intake alone is extremely rare in healthy adults because it is widely distributed in the food supply (vegetable oils, nuts, seeds, green vegetables) and stored in adipose tissue. Clinically significant deficiency occurs in specific at-risk groups:

At-Risk Group	Mechanism	Clinical Features
Fat malabsorption (any cause)	Vitamin E absorption requires micellar solubilization with fat; cystic fibrosis, cholestatic liver disease, coeliac disease, short bowel syndrome all impair this	Neurological syndrome: spinocerebellar ataxia (unsteady gait), peripheral neuropathy (loss of deep tendon reflexes, sensory loss), skeletal myopathy, pigmentary retinopathy. Often mimics Friedreich's ataxia.
Abetalipoproteinaemia	Rare genetic disorder — inability to synthesize apoB-containing lipoproteins (chylomicrons and VLDL) → fat-soluble vitamins cannot be transported from gut or liver	Severe combined fat-soluble vitamin deficiency (A, E, K especially); spinocerebellar degeneration from birth; haemolytic anaemia (PUFA in red cell membranes unprotected); acanthocytosis on blood film
Premature neonates	Limited adipose stores; immature antioxidant enzyme systems; high oxygen exposure in NICU	Haemolytic anaemia; intraventricular haemorrhage; retrolental fibroplasia (in context of hyperoxia). Prophylactic vitamin E supplementation in very premature neonates is standard care in many NICUs.
Ataxia with vitamin E deficiency (AVED)	Autosomal recessive mutation in α -TTP gene → α -tocopherol not incorporated into VLDL → systemic deficiency despite adequate intake	Progressive spinocerebellar ataxia; responds dramatically to high-dose vitamin E supplementation (800–1,200 mg/day) if started before severe neurological damage

The Supplement Paradox — Why High-Dose Vitamin E Trials Failed

The compelling mechanistic evidence for vitamin E as a protector against LDL oxidation, atherosclerosis, and cancer generated enormous enthusiasm for vitamin E supplementation in the 1990s. Multiple large RCTs subsequently failed to confirm benefit and suggested possible harm:

Trial	Dose	Population	Result
HOPE/HOPE-TOO (2000/2005)	400 IU/day natural vitamin E	High CVD risk patients, 4.5–7 years	No reduction in CVD events or cancer. HOPE-TOO: trend toward increased heart failure hospitalization.
GISSI-Prevenzione (1999)	300 mg/day	Post-MI patients	No benefit for CVD events vs omega-3 (which did benefit).
SELECT (2011)	400 IU/day vitamin E ± selenium	Healthy men, prostate cancer prevention	Vitamin E alone significantly INCREASED prostate cancer risk by 17% (HR 1.17, p=0.008).
Alpha-Tocopherol, Beta-Carotene Cancer Prevention Study (ATBC, 1994)	50 mg/day vitamin E + 20 mg/day beta-carotene	Male smokers	No lung cancer benefit from E; beta-carotene arm had 18% higher lung cancer incidence (discontinued early).
Meta-analysis (Miller et al., 2005, 135,000 patients)	High-dose (≥400 IU/day) in 19 trials	Various populations	High-dose vitamin E significantly increased all-cause mortality (dose-response relationship: higher doses → higher mortality).

WHY?

Why did vitamin E supplements fail to replicate the protection observed with dietary vitamin E intake? Several explanations: (1) Pharmacological doses of a single tocopherol form displace other tocopherols from tissues — particularly gamma-tocopherol, which may have anti-inflammatory properties independent of antioxidant activity. (2) The oxidative environment in which vitamin E acts in vivo is far more complex than can be addressed by supplementing one antioxidant. (3) The protection from dietary vitamin E comes with the full food matrix (other antioxidants, polyphenols, minerals) rather than isolated alpha-tocopherol. (4) High-dose antioxidants may impair adaptive physiological responses to oxidative stress (hormesis) that are protective in small amounts. The lesson is the same as for beta-carotene: food-derived vitamin E is beneficial; pharmacological isolated supplementation is not and may be harmful.

PRACTICE

Vitamin E supplementation recommendations: For most adults, dietary sources are adequate (RDA: 15 mg/day alpha-tocopherol — met by: 2 tablespoons sunflower oil, 30g almonds, or 100g sunflower seeds). Supplementation indicated for: fat malabsorption conditions (50–400 IU/day, water-miscible form); ARED (800–1,200 mg/day); premature infants. Do NOT recommend high-dose vitamin E supplements (≥400 IU/day) for CVD, cancer, or anti-ageing purposes — evidence of harm. Drug interaction: doses >400 IU/day may potentiate warfarin anticoagulation; monitor INR if combined.

VITAMIN K — Coagulation, Bone and Beyond

Vitamin K is a fat-soluble vitamin named from the Danish 'Koagulation' — reflecting its first recognized function in blood clotting. It exists in two major dietary forms: vitamin K1 (phylloquinone, from plant sources) and vitamin K2 (menaquinones MK-4 to MK-13, from animal sources and fermented foods and synthesized by gut bacteria). A synthetic form K3 (menadione) is no longer used clinically due to toxicity.

Vitamin K

Carboxylation, the Coagulation Cascade, Bone Mineralisation & Vascular Protection

Functions: The Carboxylase Reaction

Vitamin K's function is elegantly specific: it is the essential cofactor for gamma-glutamyl carboxylase (GGCX), the enzyme that carboxylates specific glutamate (Glu) residues in vitamin K-dependent proteins to gamma-carboxyglutamate (Gla). Gla residues have a unique ability to bind calcium ions, which is required for the protein's biological function. Without adequate vitamin K, these proteins are synthesized but are undercarboxylated (ucOC, des-gamma-carboxyprothrombin) and cannot function.

Vitamin K-Dependent Protein	Location	Function	Deficiency Consequence
Prothrombin (Factor II)	Liver	Coagulation: thrombin generation (cleaves fibrinogen to fibrin)	Prolonged PT/INR; haemorrhage risk
Factor VII	Liver	Extrinsic coagulation pathway initiation	Prolonged PT/INR; easy bruising, mucosal bleeding
Factor IX	Liver	Intrinsic coagulation pathway	Prolonged APTT; haemarthrosis, muscle haematoma
Factor X	Liver	Common coagulation pathway	Prolonged PT and APTT
Proteins C and S	Liver	Anticoagulants: inactivate Factors Va and VIIIa — the natural brakes on coagulation	Paradox: Protein C has a shorter half-life than prothrombin — in warfarin initiation or vitamin K deficiency, protein C falls first → transient PRO-coagulant state before anticoagulation is established
Osteocalcin (BGP)	Osteoblasts	Bone: binds hydroxyapatite crystals to collagen matrix; regulates bone mineralization quality; carboxylated osteocalcin (cOC) inversely associated with fracture risk;	Impaired bone mineralization (independent of vitamin D effects); elevated ucOC associated with T2DM

		undercarboxylated osteocalcin (ucOC) is a metabolic hormone (stimulates insulin secretion and muscle glucose uptake)	risk and metabolic dysfunction
Matrix Gla Protein (MGP)	Vascular smooth muscle, cartilage	Potent inhibitor of arterial and cartilage calcification — carboxylated MGP binds calcium phosphate crystals and prevents deposition in vessel walls; the most powerful known inhibitor of vascular calcification	Uncarboxylated MGP (ucMGP) — the biomarker of vitamin K insufficiency — is elevated in patients with arterial calcification, CKD, and cardiovascular disease. Warfarin treatment dramatically elevates ucMGP, potentially accelerating arterial calcification as a side effect.
Gas6 (Growth Arrest-Specific protein 6)	Endothelium, nervous system	Cell survival signaling (TAM receptor ligand); involved in platelet aggregation, immune regulation, CNS myelination	Emerging evidence for roles in vascular and neurological function

WHY?

The MGP story fundamentally changes how we think about vitamin K. For 70 years, vitamin K was understood as 'the clotting vitamin' and its only clinical significance was in managing warfarin therapy and preventing neonatal haemorrhage. We now know that vitamin K2-dependent MGP carboxylation is the primary mechanism preventing arterial calcification — and that warfarin treatment, by blocking vitamin K recycling, increases ucMGP and may accelerate atherosclerosis as a long-term side effect. This creates a clinical paradox: warfarin prevents blood clots by blocking vitamin K-dependent coagulation factors, but simultaneously impairs vitamin K-dependent vascular protection. The newer anticoagulants (DOACs — rivaroxaban, apixaban, dabigatran) do not affect vitamin K and therefore do not have this side effect.

Deficiency: Who Is at Risk and Why

At-Risk Group	Mechanism	Clinical Features and Management
Newborns (especially breastfed)	Placenta poorly transfers vitamin K; breast milk very low in K1 (~1–2 µg/L vs formula: 5–10 µg/L); neonatal gut is sterile at birth (no bacterial MK synthesis); immature liver has low vitamin K-dependent factor levels	Vitamin K deficiency bleeding (VKDB, previously 'haemorrhagic disease of the newborn'): early (<24h, usually from maternal drugs); classic (1–7 days, GI/skin bleeding); late (1–3 months, particularly breastfed, often intracranial haemorrhage — most dangerous). Prevention: 1mg vitamin K1 IM at birth (100% effective) — universal recommendation WHO/AAP/ESPGHAN. Oral prophylaxis is used in some countries but less effective for late VKDB.
Fat malabsorption	All conditions impairing fat absorption impair K1 absorption; cholestasis particularly severe (K1	Prolonged PT/INR despite adequate dietary intake; bruising; mucosal bleeding. Use water-miscible (emulsified) vitamin K formulations (menadiol sodium phosphate) orally, or IV/IM K1.

	requires bile for micellar solubilization)	
Chronic antibiotic use	Broad-spectrum antibiotics reduce intestinal bacterial synthesis of MK (menaquinones); however, intestinal MK synthesis contributes <10% of vitamin K status in most individuals — effect is modest	Clinically significant mainly in patients already nutritionally marginal; not a major concern in well-nourished adults on short antibiotic courses.
Malnutrition / very low fat intake	Vitamin K1 requires dietary fat for absorption; very low-fat diets or prolonged malnutrition impair K1 absorption	Monitor INR in severely malnourished hospitalized patients; supplement if coagulopathy present.
Cholestatic liver disease	Impaired bile secretion → poor micellar solubilization of K1; hepatocellular disease also impairs synthesis of coagulation factors directly (regardless of vitamin K status)	Prolonged PT — may not correct fully with vitamin K administration if hepatocellular dysfunction is the primary cause. This distinction is the basis of the 'vitamin K response test' for PT prolongation.
Warfarin therapy	Warfarin inhibits vitamin K epoxide reductase (VKOR) → prevents recycling of vitamin K epoxide back to vitamin K hydroquinone → blocks gamma-carboxylation of all K-dependent proteins	Intentional anticoagulation effect; unintentional side effects include impaired MGP carboxylation (vascular calcification risk) and impaired osteocalcin carboxylation (bone quality effects). Warfarin patients on long-term treatment are NOT vitamin K deficient — they have adequate vitamin K but its recycling is blocked. Counsel consistent (not eliminated) dietary vitamin K intake.

The Warfarin-Vitamin K Interaction: The Most Important Drug-Nutrient Interaction in Practice

The interaction between warfarin and dietary vitamin K is the most clinically consequential drug-nutrient interaction encountered in routine nutrition practice. It is also the most mismanaged — with patients often incorrectly instructed to avoid all vitamin K-containing foods.

Common Misconception	Correct Understanding	Practical Counselling Message
'You must avoid all green vegetables on warfarin'	This is incorrect and nutritionally harmful. Green vegetables are the primary dietary K1 source and are also the primary sources of folate, magnesium, lutein, vitamin C, and anti-cancer phytochemicals. Eliminating them deprives patients of major health benefits.	'You do not need to avoid green vegetables. What matters is keeping your intake consistent from week to week. If you eat 2 cups of spinach per week normally, continue eating 2 cups per week. Sudden large changes in intake will affect your INR — but habitual consistent intake allows your anticoagulation to be dosed accurately.'
'Vitamin K is the antidote to warfarin, so eating any K will reverse anticoagulation'	Small consistent K1 intakes from food do not reverse warfarin anticoagulation — they are already	'Vitamin K from food is already factored into your warfarin dose. The danger is sudden big changes — like

	accounted for in the dose. Large acute increases (sudden consumption of very large amounts of leafy greens, vitamin K supplements, cranberry products with K) will transiently raise INR below therapeutic range.	suddenly eating a huge amount of kale every day when you normally eat very little. Consistent is the key word.'
'Vitamin K supplements are dangerous on warfarin'	Small doses of K1 (100–200 µg/day — equivalent to modest dietary K1 intake) are actually used in some anticoagulation clinics to stabilise INR variability in patients with highly fluctuating INR on warfarin.	'Vitamin K supplements are not universally forbidden, but you should discuss any supplement containing K with your anticoagulation clinic before starting.'

PRACTICE	<i>Key vitamin K counselling points for warfarin patients: (1) Consistency is the only rule — keep usual dietary habits; do not add or remove major vitamin K sources without telling the anticoagulation team. (2) Foods highest in K1: kale, spinach, Swiss chard, collards, broccoli, Brussels sprouts, parsley (all >150 µg/100g). Moderate: cabbage, lettuce, asparagus, olive oil. (3) Vitamin K2 (from fermented foods, cheese, natto) is absorbed differently and has less predictable INR effect — flag natto especially (extremely high MK-7 content: ~1000 µg/100g). (4) Supplements to watch: multivitamins containing K; 'bone health' supplements; green superfood powders. (5) The anticoagulation clinic adjusts warfarin dose to the patient's usual intake — sudden change in either direction is the problem.</i>
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EVIDENCE	<i>Vitamin K2 (MK-7) and bone health: Rotterdam Study (n=4,807, 10-year follow-up): highest vs lowest K2 intake associated with 57% lower aortic calcification and significantly lower coronary heart disease mortality. Women's Health Study and EPIC cohorts: higher K2 (not K1) intake associated with lower fracture risk and cardiovascular events. The MK-7 form (from natto and some fermented cheeses) has a much longer half-life (3 days vs 1.5 hours for K1) and better tissue penetration for bone and vascular effects. RCTs with MK-7 180 µg/day in postmenopausal women: significantly reduced vertebral bone loss at 3 years and improved arterial stiffness vs placebo (VitaK-CAC trial). Emerging clinical application: vitamin K2 supplementation as bone and vascular protection in CKD patients where calcification risk is very high.</i>
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PART FIVE — Integrated Comparison: The Four Fat-Soluble Vitamins

Feature	Vitamin A	Vitamin D	Vitamin E	Vitamin K
Active forms	Retinol, retinal, retinoic acid; RAE unit	Calcitriol [1,25(OH) ₂ D]	alpha-Tocopherol (primarily)	K1 (phyloquinone); K2 (menaquinones MK-4 to MK-13)
Primary food sources	Liver, oily fish, egg yolk, dairy (preformed); orange/yellow/dark green vegetables,	Oily fish, egg yolk, fortified dairy; primarily cutaneous UVB synthesis	Vegetable oils (sunflower, safflower, wheat germ), nuts, seeds, green vegetables	K1: leafy greens (spinach, kale, broccoli); K2: fermented foods

	red palm oil (provitamin A)			(natto, cheese), meat, egg yolk
Primary function	Vision (rhodopsin); epithelial differentiation; immunity; gene regulation	Calcium absorption (intestine); bone mineralization; PTH suppression; immune modulation	Chain-breaking lipid antioxidant in membranes and lipoproteins	Cofactor for gamma-carboxylation of Glu → Gla residues in coagulation factors, osteocalcin, and MGP
Deficiency hallmark	Night blindness → xerophthalmia; follicular hyperkeratosis; increased infection severity	Rickets (children); osteomalacia (adults); secondary hyperparathyroidism; muscle weakness	Spinocerebellar ataxia; peripheral neuropathy; haemolytic anaemia (primarily in fat malabsorption)	Bleeding (prolonged PT/INR); neonatal haemorrhagic disease; impaired bone and vascular quality (ucOC, ucMGP)
Toxicity	YES — hypervitaminosis A: hepatotoxicity, bone pain, alopecia, teratogenicity (performed only; beta-carotene safe)	YES — hypercalcaemia, nephrocalcinosis, renal failure (supplement overdose; not from sun)	Relatively low; high dose (≥400 IU/day) increases mortality and potentiates warfarin anticoagulation	Very low (no UL established; K1 and K2 non-toxic; K3/menadione was toxic but no longer used)
Primary deficiency risk populations	Children under 5 in Sub-Saharan Africa/South Asia; pregnant women; fat malabsorption; strict vegans	Breastfed infants; dark-skinned/veiled individuals; elderly; CKD; fat malabsorption; obese	Fat malabsorption; abetalipoproteinaemia; premature infants	Newborns (without IM prophylaxis); fat malabsorption; cholestasis; warfarin users
Sudan-specific relevance	VAD endemic in children and pregnant women; molokhia, pumpkin, red palm oil are key local sources; vitamin A supplementation programs ongoing	Deficiency common despite sun exposure (veiling, pigmentation, sun avoidance); no fortification program; supplement needed for high-risk groups	Deficiency rare from food; relevant in fat malabsorption (common in untreated coeliac, CF)	Neonatal IM prophylaxis critical; warfarin interaction counselling in patients on anticoagulants
Key drug interactions	Isotretinoin (synthetic retinoid: teratogen, hyperlipidaemia); oral retinoid therapy; cholestyramine (reduces absorption)	Anticonvulsants (accelerate D catabolism); glucocorticoids (impair intestinal calcium absorption); thiazides (increase hypercalcaemia risk with D supplementation); cholestyramine	Warfarin (≥1,000 mg/day potentiates anticoagulation); statin interaction minor	WARFARIN — most critical drug-nutrient interaction; consistent dietary K1 intake essential; abrupt changes destabilize INR

Assessment	Serum retinol; MRDR test; clinical staging (xerophthalmia); dietary assessment	Serum 25(OH)D (NOT 1,25(OH) ₂ D for status assessment)	Serum alpha-tocopherol (correct for lipid levels: α -tocopherol/total cholesterol ratio); haemolysis test (red cell fragility) in infants	PT/INR (coagulation function, not vitamin K stores); serum phyloquinone; ucMGP (tissue K status); ucOC (bone K status)
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Clinical Scenario: Integrated Case: Fatima, 34 Years Old, Khartoum

- Fatima is a 34-year-old woman referred to the nutrition clinic following a diagnosis of coeliac disease (confirmed by duodenal biopsy showing Marsh III changes and positive tTG-IgA antibodies). She has been symptomatic for approximately 4 years with chronic diarrhoea, bloating, and fatigue, but was only recently diagnosed. She has been on a strict gluten-free diet for 3 months and symptoms have improved. She wears full hijab and niqab and has minimal outdoor sun exposure. She is 6 weeks pregnant (her second pregnancy; she had a healthy child 3 years ago but reports the pregnancy was complicated by 'bleeding problems' after delivery). She does not smoke or drink alcohol. She is on no regular medications.
- Anthropometry: Height 161 cm; Weight 52 kg (BMI 20.1); reports losing 6 kg in the past year. Skin: follicular hyperkeratosis on upper arms. Eyes: conjunctiva appears dull. Nails: mildly pale.
- Biochemistry: Hb 98 g/L; MCV 72 fL; Serum iron 5 μ mol/L; Ferritin 6 μ g/L; Serum retinol 0.55 μ mol/L; Serum 25(OH)D 18 nmol/L; Serum alpha-tocopherol 8.1 μ mol/L (normal ≥ 12); PT 16.2 sec (normal < 13.5); INR 1.4. Serum calcium 2.1 mmol/L (low normal); ALP elevated at 180 IU/L.
- Question 1: Identify all the fat-soluble vitamin abnormalities present in Fatima. For each deficient vitamin, explain the specific mechanism by which coeliac disease caused this deficiency, linking it to the absorption physiology described in this lecture.
- Question 2: Fatima is pregnant. For each fat-soluble vitamin deficiency identified, explain the specific risk to the foetus or newborn if deficiency remains uncorrected during this pregnancy.
- Question 3: Fatima asks why she is deficient in vitamins when 'I eat healthily and I am not from a poor family.' Construct an explanation using the concepts of fat malabsorption and micellar solubilization that is accurate but accessible to a non-specialist.
- Question 4: Design a supplementation regimen for Fatima addressing all four fat-soluble vitamins, specifying: (a) form (water-miscible vs standard; D2 vs D3; K1 vs K2); (b) dose; (c) timing relative to meals; (d) duration; and (e) monitoring parameters. Justify each choice with reference to the physiology and clinical evidence.
- Question 5: Fatima's obstetric team mentions she is being considered for low-molecular-weight heparin (LMWH) rather than warfarin for anticoagulation during pregnancy due to the postpartum haemorrhage in her first pregnancy. How does the choice of LMWH vs warfarin affect your vitamin K counselling for Fatima? What is the dietitian's specific responsibility in this anticoagulation context?

Critical Thinking Questions

- This lecture demonstrates that four vitamins with very different biochemical functions share a single critical vulnerability: dependence on fat absorption. A patient with coeliac disease, Crohn's disease, cystic fibrosis, or post-bariatric surgery may present with simultaneous deficiencies in all four. Yet clinical practice often addresses these conditions one organ system at a time — GI symptoms first, nutritional deficiencies later, or not at all. What systematic approach would you implement at the point of diagnosis of a fat malabsorption condition to ensure all four fat-soluble vitamins are assessed and addressed from the outset?
- The vitamin D paradox in sun-rich countries (including Sudan): adequate UVB radiation is available but deficiency is widespread due to cultural dress practices, skin pigmentation, and behavioural factors. In a society where covering practices are both culturally important and religiously significant, how does a dietitian or public health nutritionist navigate the recommendation to increase sun exposure vs the importance of cultural respect? What population-level interventions (fortification, supplementation programs) would be more culturally appropriate and effective?
- The warfarin-vitamin K interaction is one of the most widely mismanaged drug-nutrient interactions in clinical practice — with patients routinely advised to avoid green vegetables, depriving them of folate, magnesium, vitamin C, lutein, and cancer-protective phytochemicals for years. How would you design a patient education resource (for use in a Sudanese anticoagulation clinic) that accurately communicates the 'consistency not avoidance' message in a culturally appropriate way? What are the practical barriers to implementing this approach in resource-limited settings?

Lecture Summary — Key Takeaways for Dietetic Practice

- Shared fat-soluble vitamin properties: All four require dietary fat + bile salts for micellar absorption → chylomicron transport. Any fat malabsorption condition (coeliac, CF, Crohn's, cholestasis, post-bariatric surgery) depletes all four simultaneously. All are stored (liver/adipose) — toxicity possible for A and D. Water-miscible formulations bypass micellar dependence for patients with fat malabsorption or cholestasis.
- Vitamin A: Preformed (retinol — animal sources, toxic in excess, teratogenic in pregnancy) vs provitamin A (beta-carotene — plant sources, safe, conversion down-regulated by adequate status). Three primary functions: vision (rhodopsin synthesis — night blindness is first sign), epithelial integrity (squamous metaplasia in deficiency), immune function (mucosal IgA, T-reg cells — explains increased measles mortality in VAD). VAD endemic in Sudan in children and pregnant women — molokhia, pumpkin, red palm oil are key local sources. WHO high-dose protocol for measles. Toxicity: chronic >10,000 IU/day → hepatotoxicity, fractures, teratogenicity.
- Vitamin D: Synthesis hierarchy: skin UVB (primary) → liver 25-hydroxylation [25(OH)D — the clinical measurement] → kidney 1 α -hydroxylation [calcitriol — the active hormone; regulated by PTH, FGF-23]. Classical functions: intestinal calcium absorption (calbindin synthesis), bone mineralization, PTH suppression. Non-classical: immune (TB protection, RTI prevention), muscle (fall prevention), insulin secretion, vascular health. Sudan paradox: deficient despite sun — veiling, pigmentation, sun avoidance, no dietary sources. At-risk: breastfed infants (400 IU/day from birth), elderly (800–1000 IU/day), CKD (use calcitriol directly). Toxicity: hypercalcaemia — from supplements not sun.

- Vitamin E: Alpha-tocopherol = chain-breaking membrane antioxidant (breaks lipid peroxidation cascade; regenerated by vitamin C/GSH). Deficiency rare from food; clinically significant in fat malabsorption (spinocerebellar ataxia, peripheral neuropathy), abetalipoproteinaemia, premature infants. High-dose supplements (≥ 400 IU/day): RCTs show no CVD or cancer benefit; SELECT trial showed increased prostate cancer risk; meta-analysis showed increased all-cause mortality. Drug interaction: potentiates warfarin at ≥ 1000 mg/day.
- Vitamin K: Cofactor for gamma-carboxylation of Glu $\rightarrow$ Gla. Targets: coagulation factors (II, VII, IX, X, proteins C and S — bleeding if deficient); osteocalcin (bone mineralization quality); Matrix Gla Protein (MGP — arterial calcification prevention — warfarin blocks this, potentially accelerating atherosclerosis as a side effect). Neonatal IM prophylaxis (1 mg K1) prevents VKDB. Warfarin interaction: CONSISTENCY not avoidance of dietary K1 — patients must not be told to eliminate green vegetables. K2 MK-7 evidence for bone and vascular protection in CKD and postmenopausal women.

Suggested reading:

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Module 1 — Micronutrients & Protective Elements

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

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Water-Soluble Vitamins: B-Complex · Vitamin C

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

- ▶ Part 1: The B Vitamins as Energy & Cell Builders
- ▶ B1 Thiamin | B2 Riboflavin | B3 Niacin | B5 Pantothenic Acid
- ▶ B6 Pyridoxine | B7 Biotin | B9 Folate | B12 Cobalamin
- ▶ Part 2: The One-Carbon Network — Folate, B12 & B6 Working Together
- ▶ Part 3: Vitamin C — Beyond Antioxidant
- ▶ Part 4: Integrating the Lecture — When Multiple B Vitamins Are Deficient

Water-Soluble Vitamins

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

Focus: Understanding causes, risk factors & dietary implications — not memorizing biochemical pathways

How to Read This Lecture?

The original lecture on water-soluble vitamins was built for biochemists. This version is built for clinical dietitians. Every B vitamin and vitamin C is presented through four questions that will guide your practice for the rest of your career:

The Four Clinical Questions	What Each Question Unlocks
1. What does this vitamin actually do — in plain terms?	Gives you the conceptual anchor. You do not need to memorise every enzyme; you need to understand what breaks down when this vitamin is missing.
2. What factors affect how much of it the body absorbs or uses?	This is where dietary counselling lives. Food preparation, drug interactions, gut health, and life stage all change the equation.
3. Who is genuinely at risk — and why?	Moves you from population-level statistics to the real person in front of you. Risk is never random; it has identifiable causes.
4. What does deficiency look like — and what is the dietitian's response?	Connects biochemistry to the clinical encounter. You should be able to explain why a symptom occurs, not just list it.

One principle runs through this entire lecture: water-soluble vitamin deficiency is almost never about ignorance of what to eat. It is about absorption barriers, increased demand, or conditions that destroy or excrete the vitamin faster than it can be replaced. Your job is to find the reason — not just prescribe the food.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain in plain language what each water-soluble vitamin enables the body to do — and what fails when it is missing
- Identify the key dietary, physiological, and medical factors that increase or reduce a person's effective vitamin status
- Recognize high-risk populations for each deficiency and explain the specific reason each group is vulnerable
- Connect deficiency signs and symptoms to their underlying cause — not merely list them
- Formulate evidence-based dietary recommendations that account for bioavailability, food preparation, and individual risk factors
- Distinguish between conditions where food-based intervention is sufficient and those requiring clinical supplementation

PART ONE — The B Vitamins as Energy & Cell Builders

Think of the B vitamins not as isolated nutrients but as a coordinated team. Their central job is to keep two fundamental processes running: energy production from food, and the continuous renewal of cells. These two jobs explain almost every deficiency symptom you will ever see.

Vitamin B1 — Thiamin

The Gateway Vitamin for Carbohydrate Energy

What Does It Do?

Thiamin's essential job is to unlock the energy stored in carbohydrates and make it available to cells — particularly brain cells and nerve fibers, which cannot run on anything else and cannot store their own fuel supply. When thiamin is low, the body can still partially digest carbohydrates, but it cannot complete the conversion to usable energy. The result is that cells — especially neurons — begin to starve even when the person is eating.

WHY?

This is why every symptom of thiamin deficiency is neurological or cardiac. The brain fails when it cannot access glucose energy. The heart, which also has a very high energy demand, develops abnormal rhythms and eventually high-output failure. These are not random consequences — they follow directly from the vitamin's function.

Factors That Affect Thiamin Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Raw freshwater fish & shellfish	Destroys thiamin	Thiaminase enzymes in raw fish inactivate the vitamin before absorption — a clinically significant issue in populations with high raw fish consumption
Tea, coffee, betel nut	Reduces absorption	Contain anti-thiamin compounds (polyphenols) that chemically inactivate thiamin in the gut
Milling and food processing	Major loss	Up to 80% of thiamin is lost when whole grains are refined to white rice or white flour — the single largest dietary cause of population-level deficiency
Alcohol (chronic use)	Triple mechanism	Reduces dietary intake; damages gut absorption; impairs the liver's ability to store and activate the vitamin. All three operate simultaneously.
Cooking in large volumes of water	Leaches out	Thiamin is highly water-soluble; boiling and discarding cooking water removes a substantial proportion

High-carbohydrate diet without sufficient thiamin	Increases demand	More carbohydrate intake requires more thiamin to process it — a diet high in refined carbs with low thiamin creates a functional deficit faster
Diuretics, particularly furosemide	Urinary loss	Increases renal excretion of thiamin; a significant and often overlooked risk in cardiac patients on diuretic therapy

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
People with alcohol use disorder	Simultaneously reduced intake, impaired gut absorption, and impaired hepatic activation — the most severe and common cause of clinical thiamin deficiency in high-income countries	Wernicke's encephalopathy: sudden confusion, inability to control eye movements, unsteady gait — a medical emergency
Communities eating predominantly polished white rice	Thiamin stripped in milling; not replaced if fortification absent — the historical cause of epidemic beriberi across Asia	Peripheral numbness, tingling, leg weakness (dry beriberi); or swollen legs and breathlessness (wet beriberi)
Patients receiving IV glucose without thiamin supplementation	IV glucose rapidly consumes the remaining thiamin reserves in a person who is already depleted	Acute onset of Wernicke's encephalopathy; this is a preventable medical error — thiamin must always be given before glucose in at-risk patients
Cardiac patients on long-term diuretics	Furosemide accelerates urinary thiamin loss; rarely screened or supplemented	Unexplained worsening of heart failure; fatigue disproportionate to cardiac status
Patients post bariatric surgery	Reduced food intake, altered gut anatomy, vomiting — all reduce thiamin absorption	Rapid-onset neurological symptoms post-surgery; one of the most common post-bariatric nutritional emergencies

Clinical Scenario: A Dietary Pattern Review

- A 42-year-old man with heart failure is prescribed furosemide 80mg daily. He reports fatigue and tingling in his feet. His diet consists mainly of white rice, bread, and tea throughout the day.
- What three features of this history point to thiamin deficiency? Why would his cardiologist be unlikely to consider thiamin as a cause? What dietary and supplementation guidance would you provide — and why does the order of intervention matter?

PRACTICE

Your dietary recommendation is not simply 'eat more whole grains.' You must first assess the cause of the deficit. If absorption is impaired, food changes alone are insufficient. If diuretics are the cause, supplementation is essential alongside diet. Always ask: is the barrier to thiamin adequacy in the mouth, the gut, the liver, or the kidney?

Vitamin B2 — Riboflavin

The Gateway Nutrient That Activates Other B Vitamins

What Does It Do?

Riboflavin performs two interconnected roles. First, it serves as the core working molecule in the enzymes that extract energy from fats, carbohydrates, and protein — its active forms (FAD and FMN) physically carry electrons during energy production. Second — and this is what makes riboflavin uniquely important — it is required to chemically activate several other B vitamins into their working forms. Without adequate riboflavin, vitamins B6, folate, and niacin cannot function properly even if they are present in the diet.

WHY?

This is why riboflavin deficiency has a multiplier effect. A person with borderline riboflavin inadequacy may present with signs that look like B6 deficiency, folate deficiency, or niacin deficiency — because all three depend on riboflavin for activation. Treating only the downstream deficiency without correcting riboflavin status is clinically incomplete.

Factors That Affect Riboflavin Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Light exposure	Destroys riboflavin rapidly	Milk stored in clear glass or transparent packaging loses significant riboflavin within hours of light exposure — a major unrecognized source of loss
Milk and dairy avoidance	Removes primary dietary source	Dairy products contribute the largest share of riboflavin in most diets; vegans and lactose-intolerant individuals with no dairy equivalent are at risk
Oral contraceptives and some antidepressants	Increase demand or impair metabolism	Several medications alter riboflavin metabolism; women on long-term oral contraceptives may have functional riboflavin insufficiency without overt deficiency
Thyroid hormone insufficiency	Impairs conversion to active forms	Hypothyroidism reduces the efficiency of converting dietary riboflavin into FAD and FMN — a diet-laboratory disconnect that is rarely investigated
Intense physical exercise	Increases demand	Athletes, particularly endurance athletes, have elevated riboflavin turnover; standard dietary reference values may be insufficient for high training loads
High alcohol intake	Impairs absorption	Damages the gut mechanisms that absorb riboflavin; often compounded by poor diet quality

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
Vegans and dairy-avoiders without alternative sources	Dairy is the primary riboflavin source in most diets; plant sources exist (almonds, mushrooms, leafy greens) but provide lower amounts — dietary planning is essential	Cracking at corners of the mouth (angular cheilitis), sore tongue, sensitivity to light — often misattributed to iron or zinc deficiency
Women of reproductive age on oral contraceptives	Hormonal effects on riboflavin metabolism may create functional insufficiency even with adequate intake	Fatigue, mouth lesions, and dermatitis that do not respond to iron supplementation
People with hypothyroidism	Thyroid hormones are needed to convert riboflavin to its active coenzyme forms; hypothyroidism creates a metabolic conversion failure	May present as unexplained fatigue and poor response to other B vitamin repletion
Anyone with a confirmed B6, folate, or niacin deficiency	The downstream deficiency may be caused or worsened by riboflavin insufficiency — assess riboflavin status before or alongside the other B vitamins	Failure to respond to targeted B6 or folate supplementation

PRACTICE

When a patient has confirmed B6 or folate deficiency, always consider riboflavin status — particularly if supplementation of the downstream vitamin produces an incomplete response. This gateway relationship between riboflavin and the other B vitamins is one of the most clinically underappreciated interactions in nutrition practice.

Vitamin B3 — Niacin

The Energy Carrier Vitamin — and the Diet-Disease Link

What Does It Do?

Niacin's active forms (NAD and NADP) are the most used electron-carrying molecules in the entire body — involved in over 500 metabolic reactions. In practical terms, niacin enables three things: the extraction of energy from all three macronutrients; the building of fatty acids and cholesterol; and the repair of DNA damage. A unique feature of niacin is that the body can manufacture a small amount from the amino acid tryptophan — but only if several other nutrients (B2, B6, iron) are present to run the conversion pathway.

WHY?

This tryptophan-to-niacin pathway is why pellagra — the classic niacin deficiency disease — is not simply a matter of eating too little niacin. It emerges when multiple dietary inadequacies overlap: low tryptophan, low B2, low B6, and low niacin simultaneously. This makes pellagra a disease of dietary pattern, not of a single nutrient.

Factors That Affect Niacin Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Maize (corn) as a dietary staple without nixtamalisation	Blocks niacin availability	Maize contains niacin chemically bound to a compound (niacytin) that the human gut cannot release; traditional nixtamalisation (treating maize with lime water) breaks this bond and releases niacin — this is why pellagra historically affected people who adopted maize without this preparation technique
Low protein / low tryptophan diet	Reduces endogenous niacin synthesis	The body's only alternative niacin source is tryptophan from dietary protein; diets low in animal or complete protein reduce this pathway
Riboflavin and B6 insufficiency	Impairs tryptophan conversion	The conversion of tryptophan to niacin requires B2 and B6 as cofactors — multiple B vitamin inadequacies compound each other
Carcinoid tumour	Diverts tryptophan	This tumor converts tryptophan to serotonin rather than niacin — a metabolic diversion that can produce clinical niacin deficiency even with adequate dietary intake
Isoniazid (TB treatment)	Structural interference	Isoniazid is chemically similar to niacin and blocks niacin metabolism — patients on long-term isoniazid therapy for tuberculosis are at risk of iatrogenic pellagra
Alcohol use disorder	Combined dietary and metabolic impairment	Typically low dietary intake of protein and niacin; plus impaired B2 and B6 status further blocks the tryptophan conversion pathway

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
Communities eating un-nixtamalised maize as a staple	A dietary pattern, not a single food choice — pellagra historically affected communities that adopted maize farming without transferring the traditional lime-soaking preparation method	Classic pellagra: skin that darkens and peels where exposed to sunlight (Casal's necklace around the neck), diarrhoea, confusion — the 4 Ds (dermatitis, diarrhoea, dementia, death if untreated)
People with alcohol use disorder	Low protein intake, low B2 and B6 (impairs tryptophan conversion), often low overall food variety	Skin rash in sun-exposed areas; cognitive symptoms; may coexist with thiamin deficiency — assess all B vitamins together
Patients on long-term isoniazid (TB treatment)	Drug-nutrient interaction that blocks niacin metabolism — an iatrogenic cause often missed because the skin rash is attributed to drug side effects	Dermatitis and confusion in a TB patient — always consider niacin status alongside isoniazid
People with malabsorption disorders or severe protein-energy malnutrition	Inadequate tryptophan, impaired absorption of all B vitamins	May present as part of a complex multi-nutrient deficiency — difficult to isolate clinically

PATIENT

In Sudan and East Africa, where sorghum and millet (which do not require nixtamalisation) have historically been the staple grains, pellagra is less common than in regions where maize became dominant without the associated food preparation traditions. However, dietary transitions toward processed maize products without fortification may increase risk.

Vitamin B5 — Pantothenic Acid

The Universal Vitamin — CoA, Energy Metabolism, Fat Synthesis & Wound Healing

Pantothenic acid is one of the most universally present vitamins in the food supply — its name comes from the Greek word meaning "from everywhere." This reflects reality: it is found in meaningful amounts in virtually every food group. Its active form, Coenzyme A (CoA), is the body's primary carrier of acyl and acetyl groups — the two-carbon units that enter the TCA cycle for energy, build fatty acids and cholesterol, and form steroid hormones. A second active form, acyl carrier protein (ACP), carries the growing fatty acid chain during fat synthesis. Together these forms make B5 essential for extracting energy from all three macronutrients and for building the lipid structures every cell membrane requires.

WHY?

This explains why B5 deficiency is almost never seen in isolation from general malnutrition — the body protects CoA availability at the expense of almost everything else. When experimental depletion is induced in volunteers, the first and most specific symptom is a painful burning sensation in the feet (burning feet syndrome) — reflecting the peripheral nerves' dependence on CoA for myelin maintenance. In clinical practice, B5 matters less as an isolated deficiency and more as part of the complete B vitamin picture in alcohol use disorder, severe malnutrition, and prolonged parenteral nutrition.

Factors That Affect Pantothenic Acid Status

- Food processing: Up to 75% of pantothenic acid is lost when whole grains are milled to white flour; significant losses also occur in canning and freezing. The shift to heavily processed diets reduces B5 intake, though frank deficiency remains rare because the vitamin is so ubiquitous in whole foods.
- Alcohol use disorder: Chronic alcohol use impairs B5 absorption and increases urinary excretion — adding to the multiple B vitamin deficits characteristic of this condition. Include B5 in comprehensive B vitamin repletion protocols for patients with alcohol use disorder.
- Severe malnutrition or prolonged parenteral nutrition without supplementation: In near-total dietary deprivation, B5 stores are depleted within weeks. Standard TPN formulations include pantothenic acid — its omission rapidly impairs CoA-dependent metabolism throughout the body.
- Best dietary sources: Organ meats (liver, kidney — richest sources), chicken, beef, eggs, avocado, mushrooms (especially shiitake), sweet potato, sunflower seeds, legumes, yogurt, and whole grains. Adequate Intake (AI): 5 mg/day for adults. No established Tolerable Upper Intake Level — no toxicity observed even at very high supplemental doses.

When B5 Status Becomes Clinically Relevant

- Burning feet syndrome: The first and most specific sign of B5 deficiency — a painful burning and numbness in the feet, documented in prisoners of war on severely restricted diets and reproducible by deliberate experimental depletion. It resolves rapidly with B5 repletion and reflects peripheral nerve dependence on CoA for myelin maintenance.
- Wound healing: Pantothenol (dexpanthenol — the provitamin form of B5) is used topically in wound care formulations, nappy rash creams, and skin barrier products. It accelerates re-epithelialization and improves wound closure by supporting CoA-dependent fatty acid synthesis needed for membrane repair. This is one of the most evidence-based topical applications of any B vitamin and is familiar to most nurses and pharmacists as D-Panthenol or Bepanthen.
- Lipid management: Pantethine (a metabolite of B5, distinct from standard pantothenic acid) at 600–900 mg/day has demonstrated modest but real LDL-C and triglyceride reduction in RCTs — through effects on CoA-dependent cholesterol and fatty acid synthesis. Effect is smaller than statin therapy but may be clinically useful in patients with mild dyslipidaemia who decline pharmacological treatment. Note: standard pantothenic acid supplements at RDA doses do not have this lipid-lowering effect — pantethine is the specific active form studied.

PRACTICE

For most patients, B5 requires no specific dietary counselling — adequate intake is virtually guaranteed by any diet containing animal protein, legumes, or whole grains. Clinically, focus on three situations: (1) alcohol use disorder — include B5 in the complete B vitamin repletion protocol; (2) patients with wounds, burns, or post-surgical skin breakdown — topical dexpanthenol (Bepanthen, D-Panthenol) has genuine RCT evidence for accelerating wound healing and is safe for all patient groups; (3) patients with mild dyslipidaemia seeking non-pharmacological options — pantethine specifically (not standard B5 supplements) at 600–900 mg/day has modest but consistent LDL and triglyceride-lowering evidence across several RCTs.

Vitamin B6 — Pyridoxine

The Amino Acid Vitamin — Neurotransmitters, Blood & Immunity

What Does It Do?

Vitamin B6, in its active form PLP, is the body's primary tool for working with amino acids. Any time the body needs to convert one amino acid into another, build a neurotransmitter from an amino acid, make haem for red blood cells, or clear homocysteine from the blood, it requires B6. This explains why B6 deficiency produces such a diverse set of problems: it affects the brain (neurotransmitter synthesis), blood (haem production), and cardiovascular risk (homocysteine accumulation) simultaneously.

WHY?

Serotonin (mood and sleep), dopamine (motivation and movement), GABA (calmness and anxiety control), and norepinephrine (stress response) are all built from amino acids using PLP as the key tool. A person with B6 deficiency will not have a single, clearly identifiable symptom — they may present with depression, irritability, sleep disturbance, and fatigue simultaneously, none of which by itself points clearly to B6.

Factors That Affect Vitamin B6 Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Oral contraceptives	Increase B6 requirement	Oestrogen increases the metabolism of tryptophan through a pathway that competes with PLP — effectively raising the demand for B6 in women taking hormonal contraceptives
High protein intake	Increases demand	More protein in the diet means more amino acid metabolism — and more B6 required to process it; high-protein diets without a corresponding increase in B6 intake can create functional insufficiency
Food processing and cooking	Reduces availability	PLP is heat-labile and water-soluble; significant losses occur in canning, boiling, and prolonged cooking; bioavailability of plant-food B6 is also lower than from animal sources

Isoniazid and several anticonvulsants	Block PLP function	These drugs bind to or chemically inactivate PLP — patients on long-term isoniazid or anticonvulsant therapy require B6 assessment and often supplementation
Alcohol use disorder	Multiple mechanisms	Alcohol metabolites directly inactivate PLP; poor dietary quality; increased urinary loss — B6 deficiency is almost universal in chronic alcohol use disorder
Kidney disease (on dialysis)	Losses during treatment	Dialysis removes water-soluble vitamins from the blood; B6 supplementation is standard practice in dialysis patients

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
Women on oral contraceptives	Increased metabolic demand — not impaired absorption	Depression, irritability, and sleep disturbance that develop or worsen after starting contraception; often not investigated nutritionally
People with alcohol use disorder	Active destruction of PLP by alcohol metabolites, combined with poor dietary intake	Peripheral neuropathy (tingling, burning feet), dermatitis around eyes and mouth, microcytic anaemia that does not respond to iron
Patients on isoniazid or anticonvulsants	Direct drug-nutrient interaction blocking PLP activity	Peripheral neuropathy in a TB or epilepsy patient — B6 supplementation is recommended as a routine co-prescription with isoniazid in many guidelines
Elderly individuals	Reduced absorption efficiency and often lower dietary protein (and therefore lower B6 intake)	Subtle cognitive decline, increased infection susceptibility, and elevated homocysteine — all may partly reflect B6 insufficiency

CAUTION

Megadose B6 supplementation (above 100-200 mg/day chronically) causes a paradoxical sensory neuropathy — the same symptom that B6 deficiency causes. This reversal of effect is rare with food sources but occurs with high-dose self-prescribed supplements. Always establish the dose and duration before attributing neuropathy to deficiency or excess.

Vitamin B7 — Biotin

The Fat and Glucose Building Vitamin

What Does It Do?

Biotin's job is straightforward: it powers four specific enzyme reactions that build and interconvert fats and glucose. Of these, the most clinically important is its role in gluconeogenesis — the liver's ability to make new glucose when blood sugar is low. Biotin deficiency is rare because it is found in almost all foods and because intestinal bacteria produce it. When it does occur, it produces a highly distinctive pattern: hair loss, a characteristic rash around the eyes, nose and mouth, and neurological symptoms — all of which reverse rapidly with biotin repletion.

WHY?

The hair and skin symptoms of biotin deficiency reflect how the body prioritizes its limited supply. When biotin is scarce, it is directed to the most metabolically critical functions first; hair follicles and skin cells — which divide rapidly and require substantial biotin — are effectively rationed last. This is why hair and skin are the earliest visible signs of deficiency.

Factors That Affect Biotin Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Raw egg white consumption (large amounts)	Blocks biotin absorption	Avidin, a protein in raw egg white, binds biotin with extraordinary affinity and prevents it from being absorbed; cooking denatures avidin completely and eliminates this risk
Long-term antibiotic use	Reduces gut bacterial contribution	Gut bacteria synthesize meaningful amounts of biotin; broad-spectrum antibiotics that disrupt the microbiome reduce this supply — relevant particularly in people on prolonged antibiotic courses
Biotinidase deficiency (genetic)	Prevents recycling	An inherited condition in which the enzyme that recycles biotin from protein breakdown does not function; identified by newborn screening in many countries; requires lifelong supplementation
Pregnancy	Increases demand	Biotin turnover accelerates during pregnancy; subclinical biotin deficiency is more common in pregnancy than generally Recognize d and may contribute to pregnancy-related hair thinning
Parenteral nutrition without biotin supplementation	Removes dietary source entirely	Patients on prolonged TPN who do not receive biotin supplementation develop deficiency — now standard to include in TPN formulations

PATIENT

A patient present with hair loss, a red scaly rash around the eyes and nose, and fatigue. Before prescribing biotin supplements, ask: are they consuming large quantities of raw egg white? Are they on long-term antibiotics? Do they have a family history of biotinidase deficiency? Most biotin deficiency has an identifiable, modifiable cause.

Folate (Vitamin B9)

The Cell Renewal Vitamin — and the Most Critical Periconceptual Nutrient

What Does It Do?

Folate has one primary job: enabling cells to copy and repair their DNA so that they can divide. Every rapidly dividing cell in the body — red blood cell precursors in the bone marrow, the cells of the developing embryo's neural tube, and the cells that line the gut — depends on folate to complete division. When folate is inadequate, cell division slows or stalls, and abnormal, oversized cells accumulate. The consequences appear first wherever cell division is fastest.

WHY?

The connection between folate and neural tube defects (NTDs) is the most consequential nutritional discovery of the 20th century. The neural tube — which forms the brain and spinal cord — closes during the first 28 days after conception, before most women know they are pregnant. If folate is inadequate during those 28 days, the tube may fail to close completely, resulting in spina bifida or anencephaly. This is why folate supplementation must begin before conception, not after a pregnancy is confirmed.

Factors That Affect Folate Status

Factor That Affects This Vitamin	Effect	Why It Matters to You as a Dietitian
Cooking	Destroys 50-90% of food folate	Folate in vegetables is highly heat-labile and water-soluble; boiling leafy greens for extended periods can eliminate nearly all the folate present. Steaming, microwaving, or eating raw preserves far more.
Alcohol consumption	Triple impairment	Reduces dietary folate intake; impairs absorption in the small intestine; and causes the liver to release stored folate abnormally, leading to increased urinary excretion
MTHFR gene variant (C677T)	Reduces metabolic efficiency	This extremely common genetic variant reduces by 40-70% the efficiency of converting folate to its active form. People with this variant have higher folate requirements and elevated homocysteine — without knowing why unless tested.

Methotrexate, trimethoprim, and some anticonvulsants	Directly block folate metabolism	These drugs work partly by interfering with folate pathways; patients on long-term methotrexate (for rheumatoid arthritis, psoriasis) require folate supplementation to prevent deficiency
Folic acid vs food folate — bioavailability difference	Synthetic form is more bioavailable	Folic acid (the synthetic form in supplements and fortified foods) is absorbed approximately 1.7 times more efficiently than folate from food — relevant when calculating whether a person's intake meets their actual requirement
Malabsorption — coeliac disease, Crohn's, inflammatory bowel disease	Damaged gut cannot absorb folate	Folate absorption occurs in the proximal small intestine — the same area most affected by coeliac disease. Any patient with uncontrolled coeliac disease will have compromised folate status regardless of dietary intake.

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
Women of reproductive age who may become pregnant	The neural tube closes before pregnancy is confirmed; relying on post-conception supplementation is too late — folate adequacy must be established before conception	Neural tube defects (spina bifida, anencephaly) in the newborn — largely preventable with adequate periconceptional supplementation
People with the MTHFR C677T genetic variant	Reduced metabolic conversion efficiency means standard dietary intake may not produce adequate active folate — a genetic risk factor present in 10-15% of many populations	Elevated homocysteine without clear dietary deficiency; poor response to dietary folate alone — may require methylfolate supplementation specifically
People with coeliac disease — controlled or uncontrolled	Even controlled coeliac disease may involve residual absorption impairment in the proximal small intestine where folate absorption occurs	Macrocytic anaemia; elevated homocysteine; fatigue — often attributed to iron deficiency in coeliac patients when folate is the actual or co-contributing deficiency
People with alcohol use disorder	All three mechanisms simultaneously — reduced intake, impaired absorption, increased urinary excretion	Megaloblastic anaemia (large, immature red blood cells); elevated homocysteine
Patients on methotrexate or long-term anticonvulsants	Drug-folate interaction that mimics or induces deficiency	Fatigue, mouth sores, and elevated homocysteine in a patient on methotrexate — folate supplementation (as folinic acid, not folic acid, for methotrexate patients) is standard of care

PRACTICE

Population-level folate supplementation through food fortification has been implemented in over 80 countries and has reduced NTD rates by 25-50% where implemented. In countries without mandatory fortification, preconception counselling about folic acid supplementation is the primary prevention tool — and it must begin before the woman considers herself pregnant.

Vitamin B12 — Cobalamin

The Animal-Food Vitamin — Nerve Protection & the Folate Partner

What Does It Do?

Vitamin B12 performs two distinct jobs in the body. First, it works alongside folate in the cell renewal pathway — specifically, it is needed to convert folate into the form that cells can actually use for DNA synthesis. Second, it maintains the protective myelin sheath that insulates nerve fibers throughout the brain and spinal cord. The folate job explains why B12 deficiency causes anaemia; the myelin job explains why B12 deficiency causes neurological damage that folate supplementation cannot prevent or reverse.

WHY?

B12 is the only water-soluble vitamin that can be stored in substantial amounts in the liver — typically 2-5 years' worth. This means that deficiency develops slowly and is often silent for years before symptoms appear. By the time neurological symptoms emerge, significant myelin damage may already have occurred — some of which is irreversible. This is why identifying risk before deficiency is fully established matters more for B12 than for almost any other nutrient.

The Absorption Story — Why B12 Deficiency Is Often Not About Diet

B12 has by far the most complex absorption pathway of any vitamin, involving at least five specific steps that can each fail independently. Understanding this pathway is essential for dietitians because it means that B12 deficiency is frequently NOT caused by inadequate dietary intake — it is caused by an absorption failure that dietary improvement alone cannot correct.

Absorption Step	What Can Go Wrong	Who This Affects
Stomach acid releases B12 from food proteins	Reduced acid (atrophic gastritis, proton pump inhibitors, H2 blockers) leaves B12 bound to food and unavailable	Elderly people with atrophic gastritis; anyone on long-term acid-suppressing medication
Gastric parietal cells secrete Intrinsic Factor (IF)	Autoimmune destruction of parietal cells eliminates IF production — pernicious anaemia	Older adults, particularly those with autoimmune conditions or Northern European ancestry

IF-B12 complex travels to terminal ileum for absorption	Ileal disease, resection, or Crohn's disease removes the absorption site	Crohn's disease patients; anyone who has had ileal resection
Pancreatic proteases release B12 from its temporary carrier	Pancreatic insufficiency leaves B12 bound to a carrier it cannot release in time to bind IF	Chronic pancreatitis; cystic fibrosis
Active absorption via cubilin receptor	Competition from overgrowth of gut bacteria that consume B12 before absorption (small intestinal bacterial overgrowth, SIBO)	Elderly with slow gut motility; post-surgery gut changes

WHY?

Crystalline B12 (in supplements and fortified foods) does not require gastric acid to be released — it is absorbed directly. This is why high-dose oral B12 supplementation works even in people with atrophic gastritis or who have lost Intrinsic Factor: a small fraction (about 1%) is absorbed by passive diffusion, bypassing all the machinery. At 1000mcg/day, even 1% passive absorption provides adequate daily requirements.

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
Vegans and strict vegetarians	B12 is synthesized only by microorganisms and is found exclusively in animal-derived foods. No plant food contains meaningful B12 — algae and fermented foods have been debunked as reliable sources.	Deficiency develops slowly (2-5 years to deplete liver stores); when it does, may present primarily with neurological damage (tingling, poor balance, cognitive change) before anaemia develops
Elderly people (>65 years)	Two overlapping problems: atrophic gastritis (reduced acid) impairs release of food-bound B12; and intrinsic factor secretion may decline. Up to 20% of people over 65 have evidence of B12 insufficiency.	Fatigue, cognitive decline, depression, and balance problems in an elderly person — commonly attributed to ageing rather than assessed as nutritional deficiency
Long-term users of metformin (type 2 diabetes)	Metformin blocks the calcium-dependent receptor in the ileum that enables B12 absorption — a direct drug-nutrient interaction that develops over years	Peripheral neuropathy in a diabetic patient — easily misattributed to diabetic neuropathy rather than metformin-induced B12 depletion; screening recommended after 4+ years of use
Long-term users of proton pump inhibitors (PPIs) or H2 blockers	Reduced gastric acid means B12 cannot be released from food proteins in the stomach	Gradual, insidious deficiency — particularly when combined with age-related changes in gastric function
People with autoimmune conditions — particularly autoimmune gastritis	Anti-parietal cell antibodies destroy the cells that make intrinsic factor — pernicious anaemia. The diet cannot compensate because the absorption mechanism is physically absent.	Classic pernicious anaemia: megaloblastic anaemia plus subacute combined degeneration of the spinal cord (loss of position sense, unsteady gait, spastic weakness)

RISK

The most serious clinical error in B12 deficiency management: giving folate supplements to a B12-deficient patient corrects the anaemia but does not correct — and may accelerate — the neurological damage. Folate can normalize blood cell appearance while myelin destruction continues silently. Always assess B12 before prescribing high-dose folate.

PART TWO — The One-Carbon Network: Folate, B12, and B6 Working Together

One-carbon metabolism is the name for the set of reactions through which the body moves, transfers, and uses single-carbon units for DNA synthesis and methylation (the chemical tagging of DNA, proteins, and neurotransmitters that controls gene expression). Understanding this network as a system — rather than as isolated vitamin pathways — changes how you approach several common clinical problems.

What Breaks Down	The Consequence — in Clinical Terms	The Nutrients Needed to Fix It
DNA synthesis slows	Red blood cell precursors cannot divide normally — they grow abnormally large (megaloblasts); the bone marrow is full of cells that cannot mature. Result: megaloblastic anaemia — fatigue, pallor, shortness of breath.	Folate (primary) — B12 must be confirmed sufficient before folate is supplemented alone
Methylation capacity falls	Thousands of reactions that depend on methyl group transfer are impaired — gene expression changes, neurotransmitter production slows, myelin maintenance fails	B12 (primary for methylation reactions) — folate, B6, and B2 support the broader network
Homocysteine accumulates	Homocysteine is an intermediate that should be converted onward; when any of several vitamins are insufficient, it accumulates in blood. Elevated homocysteine is independently associated with increased cardiovascular risk, thrombosis, and cognitive decline.	B12, folate, B6 — all three are needed to clear homocysteine through different pathways
Neural tube fails to close (in embryo)	The most catastrophic consequence of inadequate folate in the periconceptual period — incomplete closure of the neural tube results in spina bifida or anencephaly	Adequate folate before and during the first 4 weeks of pregnancy — cannot be corrected retroactively

The practical implication for dietary assessment: when you find elevated homocysteine in a patient, it is not a B12 problem or a folate problem or a B6 problem. It is a one-carbon network problem. Investigate all three, along with B2 (which activates the folate-converting enzyme MTHFR). Supplementing only one will rarely resolve the problem fully.

PART THREE — Vitamin C: Beyond Antioxidant

Vitamin C — Ascorbic Acid

The Connective Tissue Vitamin — Collagen, Iron & Immune Defense

What Does It Do?

Vitamin C is best known as an antioxidant — but its most physiologically essential role is something quite different: it is required for the chemical reactions that stabilize collagen. Collagen is the structural protein of connective tissue — the framework of skin, blood vessel walls, bone matrix, wound tissue, and gum. Without adequate vitamin C, collagen is produced in an unstable form that breaks down. This explains every classical sign of scurvy: bleeding gums (gum tissue breaks down), poor wound healing (new collagen cannot be properly formed), fragile blood vessels (vascular walls weaken), and joint pain (cartilage and bone matrix deteriorate).

WHY?

Understanding that scurvy is a connective tissue failure — not simply a vitamin deficiency — helps explain why its symptoms take 6-8 weeks to appear after vitamin C intake stops. The body has existing collagen that must first degrade before the failure to produce new collagen becomes apparent in symptoms. It also explains why recovery is rapid with repletion: new collagen synthesis resumes quickly once vitamin C is restored.

Factors That Affect Vitamin C Status

Factor Affects Vitamin	That This	Effect	Why It Matters to You as a Dietitian
Smoking		Dramatically increases requirement	Cigarette smoke generates large quantities of free radicals that deplete vitamin C 30-40% faster than in non-smokers; the recommended intake for smokers is 35mg/day higher — but in practice, most smokers consume less, not more, vitamin C than non-smokers
Cooking and food storage		Major source of loss	Vitamin C is destroyed by heat, oxygen, and light. Boiling vegetables in large amounts of water, followed by discarding the water, can eliminate 60-80% of the vitamin C content. Cutting and storing vegetables accelerates loss through oxidation.
Alcohol use disorder	use	Reduces intake and increases requirement	Poor dietary quality, impaired absorption, and increased metabolic demand combine to make vitamin C deficiency common in people with chronic alcohol use disorder
Iron deficiency anaemia	deficiency	Reduces vitamin C's ability to help	Iron and vitamin C work together for iron absorption; vitamin C reduces iron to the form the gut can absorb. This relationship is bidirectional — improving vitamin C status often improves iron absorption, particularly from plant foods.

Inflammatory or infectious illness	Accelerates depletion	Infection, surgery, and major illness dramatically increase vitamin C turnover; critically ill patients in ICU settings may require very high supplementation to maintain adequate plasma levels
Gastrointestinal surgery	Reduces absorption surface	Particularly relevant in bariatric surgery — patients need consistent supplementation as standard care

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs to Watch For
People with very restricted dietary variety — particularly avoiding all fruit and vegetables	Vitamin C is found almost exclusively in fresh plant foods; any dietary pattern that eliminates or severely restricts these creates risk — including heavily processed food diets, extreme food selectivity, and chronic food insecurity	Early: fatigue, irritability, joint pain. Later: bleeding gums, perifollicular haemorrhages (small bleeding spots around hair follicles), poor wound healing. Full scurvy takes 6-8 weeks without vitamin C.
Elderly people, particularly isolated or institutionalized	Food preparation fatigue, dental problems that make fresh fruit and vegetables difficult to eat, poverty, and reduced appetite all reduce fruit and vegetable intake	Often presents as unexplained fatigue, bruising, and poor wound healing — frequently misattributed to normal ageing or medication effects
Smokers	The only nutrient for which smoking directly and substantially increases the dietary requirement — yet smokers typically eat fewer fruits and vegetables than non-smokers	Suboptimal status is very common; overt scurvy is rare but subclinical deficiency is not
Infants fed exclusively on boiled cow's milk	Boiling destroys all vitamin C in milk; breast milk contains adequate vitamin C; commercial formula is fortified	Infantile scurvy — swelling and pain in the legs (vitamin C is needed for bone matrix); now rare with formula use but still reported

PRACTICE

The most impactful, evidence-based dietary advice regarding vitamin C is not to eat more oranges — it is to eat fruits and vegetables with minimal cooking and maximum variety. Lightly steamed, raw, or minimally processed plant foods preserve far more vitamin C than boiled or processed equivalents. For patients who cannot achieve adequate intake through food, supplementation of 100-200mg/day is low-cost, safe, and effective.

PATIENT

Vitamin C dramatically improves non-haem iron absorption when consumed in the same meal. For a vegetarian or vegan patient struggling with iron status, recommending vitamin C-rich foods alongside iron-rich plant foods is one of the most practical and evidence-based dietary interventions available. A glass of orange juice with a lentil dish, or raw tomatoes alongside spinach, are simple and affordable examples.

Integrating the Lecture — Patterns That Matter

When Multiple B Vitamins Are Deficient

The B vitamins do not function in isolation. In practice, deficiency rarely affects only one. If a patient has confirmed folate deficiency, always assess B12, B6, and B2 — because all four interact in the one-carbon network. If a patient has confirmed B6 deficiency, always check whether riboflavin is sufficient, because B6 cannot be activated without it. The practical rule: whenever you find one B vitamin deficiency, look for its neighbors.

When Dietary Improvement Will Not Be Enough

Situation	Why Dietary Improvement Alone Fails	What Is Needed Instead
B12 deficiency due to lack of Intrinsic Factor (pernicious anaemia)	The absorption mechanism is absent — no amount of dietary B12 can compensate	High-dose oral B12 (1000mcg/day — passive absorption) or parenteral B12 injection
B12 deficiency due to metformin or PPIs	Drug is actively blocking the absorption mechanism	Remove or reduce drug if clinically possible; supplement with crystalline B12 (bypasses food-acid dependence)
Folate deficiency with confirmed MTHFR C677T homozygosity	Standard folic acid may not be efficiently converted to active methylfolate	Methylfolate (5-MTHF) supplementation rather than folic acid
Thiamin deficiency in alcohol use disorder with Wernicke's encephalopathy	Absorption is impaired; oral supplementation too slow for acute crisis	IV thiamin immediately, before any glucose is given — this is a medical emergency
Any deficiency in a patient with significant malabsorption	The gut cannot absorb what is provided orally	Parenteral supplementation, or very high oral doses designed to achieve adequate absorption through passive diffusion

Clinical Scenario: Putting It Together — A Nutritional Assessment

- A 68-year-old woman attends clinic with fatigue, tingling in her hands and feet, and a sore, smooth tongue. She has been vegetarian for 40 years and avoids dairy. She was diagnosed with type 2 diabetes 6 years ago and has been on metformin 1000mg twice daily since then. She is also on a proton pump inhibitor for heartburn. Her GP checked her folate — it was normal. He tells her the numbness must be diabetic neuropathy.
- Question 1: Why is this patient at very high risk of vitamin B12 deficiency — name all contributing risk factors.
- Question 2: Why does a normal serum folate NOT reassure you about her B12 status?
- Question 3: The GP attributed her neuropathy to diabetes. What other investigation would you request, and why?

- Question 4: If B12 deficiency is confirmed, why is simply advising her to eat B12-rich foods unlikely to help — and what would you recommend instead?
- Question 5: What other water-soluble vitamin deficiencies might she be at risk of given her overall dietary pattern, and why?

Critical Thinking Questions

- A mother asks you why she should take folic acid supplements before she is even pregnant. She says she will start as soon as she knows she is pregnant. How do you explain the 28-day window — and what barriers to preconception supplementation exist in real-world settings that make this recommendation difficult to follow?
- A patient with alcohol use disorder is admitted to hospital. The doctor orders IV glucose to address hypoglycaemia. You are the dietitian on the team. What is your immediate priority concern — and what would you communicate to the medical team before the glucose drip starts?
- Riboflavin deficiency is sometimes called a 'hidden' deficiency because it is clinically subtle and often secondary to other B vitamin deficiencies. Design a dietary assessment approach that would help you identify a patient with probable riboflavin insufficiency — without relying on laboratory tests.

Lecture Summary — Key Takeaways for Clinical Practice

- Water-soluble vitamins are rarely deficient because of ignorance — they are deficient because of absorption barriers, increased demand, drug interactions, or conditions that accelerate their loss. Finding the reason is as important as identifying the deficiency.
- Thiamin (B1): energy for the nervous system and heart; deficiency is neurological and cardiac. Alcohol, diuretics, refined carbohydrates, and raw fish are key risk factors. Wernicke's encephalopathy requires IV thiamin before glucose.
- Riboflavin (B2): activates B6, folate, and niacin. A gateway deficiency that multiplies the impact of any dietary pattern that is borderline for multiple B vitamins. Dairy avoidance and oral contraceptives are key risk factors.
- Niacin (B3): energy from all macronutrients and DNA repair. Pellagra is a dietary pattern disease — un-nixtamalised maize, alcohol, isoniazid therapy, and carcinoid tumor are the primary causes. The tryptophan-to-niacin pathway depends on adequate B2, B6, and iron.
- Folate (B9): cell division and DNA synthesis. Neural tube defects are the most consequential consequence of deficiency. Periconceptional supplementation must precede conception. Cooking, alcohol, MTHFR variants, coeliac disease, and methotrexate are major risk factors.
- Vitamin B12: nerve myelin maintenance and folate activation. Deficiency is almost always an absorption problem — not a dietary one — except in vegans. Pernicious anaemia, metformin, PPIs, and age-related gastric change are the primary clinical causes. Correcting folate without correcting B12 is dangerous.

- Vitamin C: collagen stability, non-haem iron absorption, immune function, antioxidant protection. Smoking, cooking methods, alcohol, and food insecurity are the primary risk factors. The most impactful advice is minimally processed, varied fruit and vegetable intake — and co-consumption of vitamin C with non-haem iron sources.

Suggested reading for further exploration:

1. Combs GF & McClung JP (2022). The Vitamins, 5th Ed. |
2. Stipanuk MH & Caudill MA (2019). Biochemical, Physiological & Molecular Aspects of Human Nutrition, 4th Ed. |
3. Elmadfa I & Leitzmann C. Nutrition and Health. |
4. Institute of Medicine Dietary Reference Intakes Reports.

Module 1 — Micronutrients & Protective Elements

A Clinical Reasoning Approach: Why Deficiencies Happen, Who Is at Risk & How Dietitians Respond

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Minerals & Phytonutrients

Bioavailability, Whole-Food Principles & Health-Protective Mechanisms of Plant Compounds

- ▶ The Central Insight: Eating a Mineral Is Not the Same as Absorbing It
- ▶ Part 1: Major Minerals — Calcium | Magnesium | Phosphorus
- ▶ Part 2: Trace Minerals — Iron | Zinc | Iodine | Selenium
- ▶ Part 3: Phytonutrients — Polyphenols, Carotenoids, Organosulfur Compounds
- ▶ The Whole-Food Principle: Why Pattern Beats Supplement

Minerals & Phytonutrients

A Clinical Reasoning Approach: Bioavailability, Risk Factors, Dietary Interactions & the Science of Protective Plant Compounds

Focus: Why the body cannot always access what the diet provides — and how plants protect health beyond classical nutrition

The Central Insight: Eating a Mineral Is Not the Same as Absorbing It

Unlike vitamins, minerals cannot be manufactured by the body at all — every atom of iron, zinc, calcium, or iodine must come from the diet. Yet the body absorbs only a fraction of what is eaten, and that fraction varies enormously depending on the food source, the cooking method, what else is eaten at the same meal, the person's current stores, and their physiological state. This gap between intake and absorption is called bioavailability — and it is the central concept that makes mineral nutrition genuinely complex.

WHY?

A person can have iron deficiency despite eating iron-rich foods every day. A child can develop zinc deficiency in a household that eats meat regularly. An adolescent can have calcium insufficiency while drinking milk. In every case, the question is not 'are they eating the mineral?' but 'can their body actually absorb and use it?' This is the lens through which every mineral in this lecture should be viewed.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain why bioavailability — not dietary intake alone — determines mineral status, and identify the key factors that raise or lower it
- Describe the specific dietary, physiological, and medical factors that affect absorption of iron, zinc, calcium, iodine, selenium, and magnesium
- Identify at-risk populations for each mineral deficiency and explain the mechanism behind each group's vulnerability
- Apply knowledge of mineral-mineral interactions to practical dietary counselling (iron-zinc competition, calcium-iron interference, vitamin C and iron)
- Explain what phytonutrients are, how they differ from classical nutrients, and why whole-food dietary patterns outperform isolated supplements
- Describe the main families of protective phytonutrients and connect each to a specific, evidence-based health outcome

PART ONE — Major Minerals

Major minerals are those the body requires in amounts above 100mg per day. Their functions are structural (bone, teeth), electrolyte (fluid balance, nerve transmission), and enzymatic (hundreds of reactions requiring mineral cofactors). We focus here on calcium, magnesium, and phosphorus — the bone mineral triad — with particular attention to the factors that determine whether dietary intake translates into actual adequacy.

Calcium

The Structural Mineral — Bone, Muscle & the Vitamin D Connection

What Does It Do?

Calcium has two fundamentally different jobs. The first is structural: 99% of the body's calcium forms the mineral matrix of bones and teeth, giving them rigidity and strength. The second is signaling: the remaining 1% in blood and soft tissues serves as a trigger molecule for muscle contraction, nerve impulse transmission, blood clotting, and cell-to-cell communication. The signaling function is so critical that the body will sacrifice bone calcium to maintain blood calcium within a very narrow range — which is why bone loss can occur silently for decades before it becomes clinically apparent.

WHY?

This priority hierarchy explains osteoporosis: when dietary calcium is insufficient over years or decades, the body continuously withdraws small amounts from bone to keep blood calcium stable. The individual feels nothing — blood calcium tests remain normal — while bone density quietly falls. By the time a fracture occurs, years of preventable bone loss have already happened. The clinical lesson: normal serum calcium does NOT indicate adequate calcium nutritional status.

The Bioavailability Problem — Why Source and Context Matter

Not all calcium in food is equally available for absorption. The food source, the presence of enhancers and inhibitors, and the person's vitamin D status all determine how much of the dietary calcium actually crosses the gut wall and enters the bloodstream.

Factor	Effect on Absorption / Status	Why This Matters in Practice
Vitamin D deficiency	Dramatically reduces active absorption	Vitamin D controls the proteins that transport calcium across the intestinal wall. Without adequate vitamin D, even a high-calcium diet is absorbed inefficiently — the single most important calcium bioavailability factor.
Oxalate in food (spinach, rhubarb, beet greens)	Binds calcium in the gut — nearly zero absorption	Spinach has 115mg calcium per 100g but less than 5% is absorbed due to oxalate binding. Kale and broccoli, with lower oxalate, provide 40-50% bioavailability — more than dairy in some studies.
Phytate (wholegrains, legumes)	Reduces calcium absorption	Like oxalate, phytate forms insoluble complexes with calcium. Soaking, fermentation, and sprouting reduce phytate content significantly.
High sodium diet	Increases urinary calcium loss	The kidney excretes calcium alongside sodium; a very high salt diet increases calcium excretion — a clinically significant but underappreciated contributor to calcium depletion in populations with high processed food intake.
High caffeine intake (very high doses)	Modestly increases urinary calcium loss	Effect is small and compensated by normal dietary calcium in most people, but relevant in those with very high caffeine intake and borderline calcium adequacy.
Dairy vs. plant sources	Different bioavailability	Dairy calcium: ~32% bioavailability. Low-oxalate greens (kale, bok choy, broccoli): 40-64%. High-oxalate greens (spinach): <5%. Fortified plant milks: similar to dairy if well-mixed (calcium can settle).
Age and Oestrogen status	Absorption efficiency declines	Children absorb 60-75% of ingested calcium; young adults 30-40%; postmenopausal women 20-25%. This explains why calcium requirements are highest at both ends of life and after menopause.
Calcium supplement type and timing	Carbonate requires food acid; citrate does not	Calcium carbonate (most common, cheapest) requires stomach acid for dissolution — should be taken with food. Calcium citrate is better absorbed without food and preferable for people on acid-suppressing medication or with atrophic gastritis.

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs or Consequences
Adolescent girls and young women	Peak bone mass is built between ages 9-18; inadequate calcium during this window sets a permanently lower bone density ceiling that no amount of adult supplementation can fully recover	Silent — no symptoms during deficiency; consequence is fracture risk and osteoporosis 30-40 years later
Postmenopausal women	Oestrogen maintains bone density by inhibiting osteoclast activity; its loss after menopause accelerates bone resorption at a rate that dietary calcium alone cannot fully counteract	Vertebral compression fractures (back pain, height loss), hip fractures — the leading cause of disability-related mortality in elderly women
Vegans and dairy-avoiders without planned alternatives	Dairy is the most concentrated bioavailable calcium source in most diets; plant alternatives require careful selection (low-oxalate greens, fortified milks) and consistent consumption	May develop inadequate bone mineral density over years — particularly if vitamin D status is also low
People with lactose intolerance who avoid all dairy	Lactose intolerance does not mean calcium intolerance — hard cheeses and yogurt are often well-tolerated; avoidance of all dairy without alternatives creates genuine risk	Bone density decline; increased fracture risk in middle and older age
People with vitamin D deficiency	Calcium absorption is vitamin D-dependent; even high dietary calcium intake cannot compensate for impaired absorption due to vitamin D insufficiency	Rickets in children (bone deformity); osteomalacia in adults (bone pain, muscle weakness) — both caused by failure of bone mineralization, not simply calcium deficiency

PRACTICE

The most common calcium counselling error is focusing only on the amount eaten. Equally important are: the form of calcium consumed (oxalate-bound vs. bioavailable), the vitamin D status that governs absorption efficiency, and the sodium and caffeine intake that affect retention. A patient who drinks three glasses of milk daily but is vitamin D deficient may absorb far less calcium than expected.

CONTEXT

In Sudan and much of the Middle East and Africa, dairy consumption varies widely by region and ethnicity, lactase persistence differs from European populations, and sun exposure (the primary vitamin D source) is high but skin coverage practices vary. Calcium adequacy in women of reproductive age deserves specific assessment — particularly in urban settings where dietary transition has reduced traditional food diversity.

Magnesium

The Invisible Workhorse — 300 Reactions, One Mineral

What Does It Do?

Magnesium is required as a cofactor in over 300 enzymatic reactions — more than any other mineral. Its most fundamental role is enabling every reaction that uses ATP (the body's energy currency), because ATP only functions when bound to magnesium. This means magnesium is essential for energy production, DNA replication, protein synthesis, muscle contraction, nerve transmission, and blood glucose regulation simultaneously. It is also structurally present in bone — approximately 60% of body magnesium is in the skeleton.

WHY?

Magnesium deficiency is called the 'invisible deficiency' for two reasons. First, only 1% of body magnesium is in the blood — so serum magnesium can appear normal while intracellular magnesium (where it actually works) is depleted. Second, the early symptoms — fatigue, muscle cramps, irritability, poor sleep — are so non-specific that they are attributed to stress, overwork, or other causes rather than investigated nutritionally. By the time serum magnesium falls, the deficiency is already significant.

Factors That Affect Magnesium Status

Factor	Effect on Absorption / Status	Why This Matters in Practice
Food processing and grain refining	Removes up to 80% of magnesium	Magnesium is concentrated in the bran and germ of whole grains; milling to white flour or white rice removes most of it — the dominant dietary reason for widespread low magnesium intake in populations eating refined carbohydrates
High sugar and refined carbohydrate diet	Increases urinary magnesium loss	Sugar metabolism increases renal excretion of magnesium; high-glycaemic diets are consistently associated with poorer magnesium status — a mechanistic link between diet quality and magnesium adequacy
Alcohol consumption	Triple impairment	Reduces dietary intake of magnesium-rich foods; impairs intestinal absorption; and dramatically increases renal excretion — magnesium deficiency is nearly universal in chronic alcohol use disorder
Proton pump inhibitors (long-term)	Impair intestinal absorption	PPIs reduce gastric acid, which is needed for magnesium absorption; long-term PPI use is a Recognized, FDA-acknowledged cause of severe hypomagnesaemia — often missed because serum magnesium is not routinely monitored
Type 2 diabetes and insulin resistance	Bidirectional relationship	Magnesium deficiency impairs insulin signaling and worsens insulin resistance; simultaneously, hyperglycaemia increases

		renal magnesium excretion — a vicious cycle that worsens both conditions
Diuretics (especially loop and thiazide diuretics)	Increase renal magnesium loss	Among the most common iatrogenic causes of magnesium depletion in clinical practice — patients on long-term diuretics should have magnesium monitored alongside potassium
Diarrhoea, malabsorption, short bowel syndrome	Directly reduces absorption	Any condition that accelerates gut transit or reduces absorptive surface area impairs magnesium absorption; inflammatory bowel disease is a particularly important cause

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs or Consequences
People with type 2 diabetes	Hyperglycaemia increases urinary magnesium loss while simultaneously impairing insulin function — a condition that worsens with poor glycaemic control over time	Muscle cramps, fatigue, increased insulin resistance, cardiac arrhythmias — often attributed to diabetes itself rather than investigated as a co-occurring deficiency
Patients on long-term diuretics or PPIs	Direct drug-induced renal or intestinal losses that are rarely monitored or replaced	Severe hypomagnesaemia: tetany, cardiac arrhythmias, refractory hypokalaemia (low potassium that does not correct without first correcting magnesium)
People with alcohol use disorder	All three mechanisms simultaneously — the most severe and common clinical presentation of magnesium deficiency	Muscle tremor, seizures, cardiac arrhythmias — these symptoms coexist with thiamin and folate deficiency and must be assessed together
People eating predominantly refined grains and processed foods	The modern dietary pattern in many urbanizing regions that has progressively reduced magnesium intake at a population level	Subclinical deficiency — contributing to fatigue, poor sleep, anxiety, muscle tension, and insulin resistance without a clear clinical diagnosis
Elderly individuals	Reduced dietary intake, decreased absorption efficiency, increased renal loss, and multiple medications all converge	Muscle weakness, falls, cognitive difficulties — all partially attributable to magnesium insufficiency in the elderly, rarely assessed

CONNECT

Refractory hypokalaemia — low potassium that does not correct with potassium supplementation — is a classic clinical signal of concurrent magnesium deficiency. The kidney cannot conserve potassium properly when magnesium is depleted. This is one of the most important mineral-mineral interactions in clinical practice: always check and correct magnesium when potassium will not normalise.

Phosphorus

The Energy Currency Mineral — Universally Present, Rarely Deficient

What Does It Do?

Phosphorus is the mineral backbone of ATP — every molecule of energy currency the body makes contains phosphorus. It is also structural (forming bones and teeth alongside calcium), and is embedded in the membrane of every cell as phospholipid. Unlike most minerals, phosphorus deficiency from diet alone is extremely rare because it is present in virtually all protein-containing foods. The clinical concern with phosphorus in modern diets is the opposite: excessive intake from phosphate food additives in processed foods, which can impair calcium absorption and contribute to bone loss.

WHY?

The phosphorus story reverses the usual mineral narrative. While most minerals require attention because people do not get enough, the primary concern with phosphorus in the context of modern processed food diets is that people — particularly those with kidney disease — may get too much. Phosphate additives are used extensively in processed meats, soft drinks (phosphoric acid in cola), processed cheese, and instant foods, and are absorbed far more efficiently than naturally occurring phosphorus in whole foods.

When Phosphorus Status Does Become Clinically Important

Clinical Situation	The Phosphorus Problem	Why It Matters
Refeeding syndrome (malnutrition or prolonged fasting)	When calories are reintroduced rapidly, cellular uptake of phosphorus surges — serum phosphorus falls catastrophically (hypophosphataemia)	Severe hypophosphataemia causes respiratory failure (respiratory muscles fail), cardiac arrhythmias, haemolysis, and neurological symptoms — a potentially fatal complication of poorly managed nutritional rehabilitation
Chronic kidney disease (CKD)	Failing kidneys cannot excrete excess phosphorus — it accumulates in blood (hyperphosphataemia)	Excess phosphorus binds calcium, pulls it from bone, and deposits in blood vessels and soft tissues — accelerating cardiovascular disease and bone loss simultaneously (CKD-Mineral Bone Disorder)
Premature infants	Born before phosphorus has been transferred from mother to foetus in the third trimester	Metabolic bone disease of prematurity — requires fortified breast milk or specialized formula with added phosphorus and calcium
Very low calorie diets or severe malnutrition	Severely reduced dietary intake from all sources	Muscle weakness, bone pain, impaired breathing — all reversible with careful nutritional repletion

PRACTICE

For most healthy people, phosphorus adequacy is not a concern — it is almost impossible to be deficient on any diet that provides adequate protein. The dietitian's phosphorus task is primarily about two populations: patients with CKD (restrict phosphate additives, choose whole food sources) and patients being refeed after starvation (introduce calories gradually, monitor serum phosphorus closely).

PART TWO — Trace Minerals

Trace minerals are required in amounts below 100mg per day — some in microgram quantities — yet their absence causes some of the most dramatic and consequential deficiency diseases known. Their small required amounts make them no less critical; in several cases (iron, iodine, zinc), their deficiency affects hundreds of millions of people globally and represents among the most significant nutritional public health problems of our time.

Iron

The Oxygen-Carrier Mineral — The World's Most Common Deficiency

What Does It Do?

Iron's primary job is transporting oxygen. Inside red blood cells, iron sits at the centre of haemoglobin — the protein that picks up oxygen in the lungs and delivers it to every tissue in the body. A second form, myoglobin in muscle cells, stores oxygen for immediate use during exercise. Beyond oxygen transport, iron is required for energy production in mitochondria, immune cell function, neurotransmitter synthesis (dopamine and serotonin both require iron-containing enzymes), and thyroid hormone metabolism. This breadth of function explains why iron deficiency produces such diverse symptoms.

WHY?

The neurological effects of iron deficiency — impaired attention, reduced learning capacity, and fatigue — occur even before anaemia develops. This is because the brain and developing nervous system are particularly sensitive to iron availability; neurotransmitter synthesis and myelination both require iron. In children, iron deficiency without anaemia can produce measurable cognitive impairment. Waiting for anaemia to appear before acting means the most sensitive damage has already begun.

The Bioavailability Gap — Haem vs. Non-Haem Iron

Not all dietary iron is absorbed equally. The type of iron in food determines how much the body can actually use — and this difference is large enough to change clinical recommendations entirely.

Iron Type	Food Sources	Typical Absorption Rate	Key Point
Haem iron	Red meat, poultry, fish, seafood	15-35%	Absorbed as an intact molecule — not affected by dietary inhibitors. The most bioavailable form.
Non-haem iron	All plant foods, eggs, dairy, fortified foods	2-20%	Absorption is highly variable — strongly affected by what else is eaten at the same meal. The majority of iron in most diets.

CONNECT

This bioavailability gap is why iron deficiency can occur in populations eating adequate total iron — if the iron is predominantly non-haem from plant sources, and if the diet also contains significant amounts of inhibitors (tea, coffee, phytate-rich foods). The dietitian's task is not just to assess how much iron is consumed, but what form, from what sources, with what accompaniments.

Factors That Affect Iron Absorption

Factor	Effect on Absorption / Status	Why This Matters in Practice
Vitamin C consumed in the same meal	Increases non-haem iron absorption 2-4 fold	Vitamin C reduces iron from the poorly absorbed Fe ³⁺ form to the well-absorbed Fe ²⁺ form, and keeps it soluble in the alkaline environment of the small intestine. A glass of orange juice with a lentil meal is a clinically meaningful nutritional intervention.
Tea and coffee consumed with meals	Reduces non-haem iron absorption by 60-70%	Tannins in tea and coffee bind iron and prevent absorption. This effect occurs when tea is consumed during or immediately after a meal — the same meal timing that is culturally common across much of Africa, the Middle East, and Asia.
Phytate in wholegrains and legumes	Reduces non-haem iron absorption	Phytate forms insoluble complexes with iron. Soaking, fermenting, and sprouting legumes and grains reduces phytate content and improves iron absorption — traditional food preparation methods that improved bioavailability before their nutritional logic was understood.
Calcium supplements or high calcium foods	Competes with iron absorption	Calcium directly competes with iron at the intestinal transporter. Taking calcium supplements with iron supplements or iron-rich meals reduces absorption of both. Separate by at least 2 hours.
Meat, fish, or poultry in the same meal	Enhances non-haem iron	Even small amounts of meat alongside plant-food iron enhance non-haem iron absorption through a mechanism not fully understood. A mixed diet with some animal protein significantly

	absorption (MFP factor)	improves iron status compared to a purely plant-based diet with the same total iron content.
Body iron status	The body adapts absorption to its stores	When iron stores are low, the intestine upregulates absorption — a healthy adaptive response. When stores are sufficient, absorption falls. This is why iron supplementation in iron-replete individuals produces limited additional absorption.
Inflammation and infection	Suppresses iron absorption regardless of stores	Hepcidin — the body's iron-regulating hormone — rises sharply during infection and inflammation, blocking iron absorption and keeping iron locked in storage cells. This is why treating iron deficiency anaemia in the presence of active infection is complex.

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs or Consequences
Women of reproductive age	Menstrual blood loss creates a monthly iron deficit that diet must replace. The higher the blood loss, the higher the dietary iron required — yet many women's diets are simultaneously lower in haem iron (meat) and higher in iron inhibitors (tea, coffee, phytate).	Fatigue, pallor, reduced exercise tolerance, impaired concentration — and in pregnancy, increased risk of preterm birth and low birth weight in the baby
Pregnant women	The foetus extracts substantial iron from maternal stores, and blood volume expands by 40-50% during pregnancy, requiring large amounts of additional haem iron. Dietary iron alone rarely meets this demand.	Iron deficiency anaemia in pregnancy: the most common nutritional deficiency complication of pregnancy worldwide. Supplementation is standard of care.
Infants and young children (6-24 months)	Breast milk iron content falls as the infant grows, and complementary foods in many settings are phytate-rich and iron-poor. This period represents the highest risk of iron deficiency in the entire life cycle.	Iron deficiency anaemia with cognitive impairment — the most consequential period for brain iron, as rapid neural development occurs. Some cognitive effects may be permanent.
Vegetarians and vegans	Exclusive reliance on non-haem iron with no MFP factor — and often high consumption of tea, coffee, and phytate-rich foods	Serum ferritin (iron stores) tends to be lower in vegetarians than omnivores even when haem iron intake appears adequate from non-haem sources. Requires deliberate dietary strategies.
People with inflammatory bowel disease or coeliac disease	Intestinal inflammation impairs iron absorption; blood loss through the inflamed gut adds to deficit; Hepcidin from inflammation further blocks absorption	Iron deficiency anaemia that is resistant to oral supplementation — IV iron may be required when oral iron cannot be absorbed

CONTEXT

In Sudan and sub-Saharan Africa, iron deficiency anaemia is compounded by multiple overlapping factors: high prevalence of malaria and helminth infections (both cause blood loss and raise hepcidin); diets high in phytate from sorghum, millet, and legumes; frequent tea consumption with meals; and high reproductive burden in women. The nutritional intervention must address all these factors simultaneously — dietary advice alone is insufficient without addressing infectious disease burden.

Zinc

The Growth and Immunity Mineral — the Hidden Deficiency

What Does It Do?

Zinc is a structural and catalytic component of over 300 enzymes — involved in DNA synthesis, protein production, wound healing, immune cell development, taste and smell perception, and the growth of virtually every tissue in the body. Unlike iron, zinc has no specific storage depot in the body — there is no 'zinc reserve' that can be drawn upon when intake falls. This means that zinc deficiency can develop within weeks of inadequate intake, and can be masked by the body's adaptive response of redistributing zinc from less critical to more critical tissues.

WHY?

Growth faltering is the most sensitive indicator of zinc deficiency in children — the body prioritizes other functions over growth when zinc is scarce. A child who is growing poorly despite adequate caloric intake may have zinc deficiency even without the classic signs of severe deficiency. In populations where phytate-rich plant foods dominate the diet, subclinical zinc deficiency — enough to impair growth and immunity without causing obvious clinical signs — is far more common than diagnosed deficiency.

Factors That Affect Zinc Absorption

Factor	Effect on Absorption / Status	Why This Matters in Practice
Phytate — the dominant inhibitor	Reduces zinc absorption substantially	Phytate forms very stable complexes with zinc; in diets based on unrefined grains and legumes, phytate can reduce zinc bioavailability by 45-75% compared to meat-based diets. This is the primary reason zinc deficiency is so common in plant-predominant populations even when zinc intake appears adequate.
Animal protein	Enhances zinc absorption	Animal foods provide both haem-type zinc (more bioavailable) and contain compounds that partially counteract phytate inhibition. Populations eating some animal protein alongside

		plant foods have substantially better zinc status than purely plant-based populations.
Iron supplementation in high doses	Competes with zinc absorption	Iron and zinc share the same intestinal transporter; supplemental iron (especially at doses above 25mg) can competitively inhibit zinc absorption. This is clinically relevant in pregnant women receiving high-dose iron supplements.
Fermentation, soaking, sprouting of grains and legumes	Reduces phytate — improves zinc availability	Traditional food preparation methods that reduce phytate content improve zinc bioavailability from plant foods. Leavened bread has lower phytate than unleavened bread; fermented legumes are better zinc sources than unfermented.
Calcium at high doses	Modestly reduces zinc absorption	High calcium intake (from supplements or dairy) can reduce zinc absorption — the magnitude is smaller than phytate inhibition but relevant in those taking high-dose calcium supplements

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs or Consequences
Young children in populations eating phytate-rich plant-based diets	No zinc storage; rapid growth demands continuous supply; phytate-dominated diet reduces what little zinc is present — a compound vulnerability	Growth faltering (stunting), increased frequency and severity of infections, delayed wound healing, poor appetite
Pregnant women	Foetal development and placental growth require substantial zinc; simultaneously, iron supplementation may impair zinc absorption	Increased risk of preterm birth, low birth weight, and impaired immune development in the newborn
Elderly individuals	Reduced food intake, impaired absorption, increased medication use, and lower protein intake all reduce zinc status	Impaired wound healing, increased infection susceptibility, loss of taste and smell (hypogeusia) — often attributed to 'normal ageing'
Vegetarians and vegans without dietary planning	Exclusive reliance on phytate-bound zinc from plant sources with no animal protein to counteract inhibition	Subclinical zinc insufficiency — growth faltering in children, poor immune response, delayed healing in adults
People with chronic diarrhoea or malabsorption	Zinc is lost through the gastrointestinal tract; diarrhoea is both a cause and consequence of zinc deficiency — a vicious cycle	Each episode of diarrhoea worsens zinc status; worsening zinc deficiency reduces gut integrity and immune function, making subsequent infections more severe

PRACTICE

Zinc supplementation reduces the duration and severity of diarrhoea in children — one of the most evidence-based interventions in paediatric nutrition. WHO guidelines recommend zinc supplementation as an adjunct to oral rehydration therapy for childhood diarrhoea. This is a practical clinical application of understanding the zinc-immunity-gut connection.

Iodine

The Thyroid Mineral — Brain Development and Metabolic Rate

What Does It Do?

Iodine has a single, indispensable role: it is the raw material from which thyroid hormones are built. The thyroid gland traps iodine from the bloodstream and incorporates it into the hormones T3 and T4, which regulate the metabolic rate of virtually every cell in the body — controlling energy expenditure, body temperature, heart rate, brain development, and growth. Without adequate iodine, thyroid hormone production falls, the thyroid gland compensates by enlarging (goitre), and the downstream effects of hypothyroidism develop.

WHY?

The most catastrophic consequence of iodine deficiency is not goitre in adults — it is irreversible brain damage in the developing foetus and infant. The foetal brain requires thyroid hormone for its development from the earliest weeks of gestation. If the mother is iodine deficient, the foetus cannot produce adequate thyroid hormone and brain development is permanently impaired — even if the child is supplemented after birth. This is why iodine deficiency remains the world's single most preventable cause of intellectual disability.

Factors That Affect Iodine Status

Factor	Effect on Absorption / Status	Why This Matters in Practice
Geographic location — soil and water iodine content	Determines baseline dietary iodine	Inland mountainous regions and areas far from the ocean have iodine-poor soil and water — all foods grown or raised there are iodine-poor. This is the fundamental geographic driver of endemic iodine deficiency.
Iodized salt — presence or absence in the food supply	The primary public health intervention	Universal salt iodization has dramatically reduced iodine deficiency disorders globally. Where iodized salt is not used (home cooking with non-iodized salt, processed foods made with non-iodized salt), iodine status is compromised.
Goitrogens — compounds that interfere with iodine use	Worsen deficiency in already low-iodine settings	Cassava (staple in much of sub-Saharan Africa) contains linamarin, which is converted to thiocyanate in the body — a compound that blocks iodine uptake into the thyroid. Cruciferous vegetables (cabbage, broccoli) have similar but weaker effects. These are clinically important only when iodine intake is already borderline.

Pregnancy	Substantially increases iodine requirement	The requirement increases by ~50% in pregnancy to supply the foetus and maintain maternal thyroid function. Even women with previously adequate status may become iodine-insufficient during pregnancy.
Excessive iodine intake	Can also impair thyroid function	Very high iodine intake (from certain seaweeds, or excess supplementation) can paradoxically suppress thyroid hormone synthesis — relevant in populations consuming large amounts of seaweed products

Who Is at Risk — and Why?

At-Risk Group	Core Reason	Key Signs or Consequences
Pregnant women in iodine-deficient areas	Greatly increased requirement combined with already low baseline intake	Cretinism in the child (severe intellectual disability, deaf-mutism, stunted growth) — the most severe consequence. Even mild-moderate maternal deficiency impairs child IQ by a measurable and permanent amount.
Populations in iodine-deficient geographic areas without iodized salt	No iodine in soil, water, or food; no fortification to compensate	Goitre (visibly enlarged thyroid); hypothyroidism (fatigue, weight gain, cold intolerance, cognitive slowing); intellectual disability in children born to deficient mothers
People relying heavily on cassava as a dietary staple	Cassava goitrogens worsen borderline iodine deficiency — a particularly important interaction in parts of sub-Saharan Africa	Goitre and hypothyroidism in communities where cassava is a dietary staple and iodine intake is already low
Strict vegans in iodine-deficient regions not using iodized salt	Seaweed (variable and unreliable), iodized salt, and dairy (from iodophor-sanitised equipment in some countries) are the main non-seafood sources; avoiding all of these creates risk	Subclinical hypothyroidism; in pregnancy, foetal brain impairment

CONTEXT

Iodine deficiency disorders remain endemic in parts of Sudan, particularly in inland regions away from the Red Sea coast. Goitre is visible in communities where iodized salt is unavailable or not used for home cooking. Awareness of local iodized salt availability and use in household cooking is an essential component of dietary assessment in these populations.

Selenium

The Antioxidant Mineral — Thyroid Activation and Cellular Defense

What Does It Do?

Selenium is incorporated into a family of proteins called selenoproteins — the most important of which are the glutathione peroxidases (the body's primary antioxidant enzyme system that neutralizes hydrogen peroxide and lipid peroxides) and the iodothyronine deiodinases (the enzymes that convert inactive thyroid hormone T4 into the active form T3). These two roles — antioxidant protection and thyroid hormone activation — link selenium directly to both oxidative stress disease risk and thyroid function.

WHY?

The selenium-thyroid connection is often overlooked: even when iodine intake is adequate, selenium deficiency can impair thyroid hormone activation by reducing deiodinase enzyme activity. A person can have normal thyroid gland function and adequate T4 production, yet have symptoms of hypothyroidism because insufficient T4 is being converted to the active T3 form in peripheral tissues. This is why thyroid function assessment is incomplete without considering selenium status in populations at risk of both deficiencies.

Factors That Affect Selenium Status

Factor	Effect on Absorption / Status	Why This Matters in Practice
Soil selenium content — the primary determinant	Determines selenium in all foods grown in that soil	Unlike most minerals, selenium content of plant foods varies enormously by geographic region — a function of the selenium concentration in the local soil. This makes selenium one of the most geographically variable minerals in the food supply.
Brazil nuts	Highly concentrated but variable source	Brazil nuts contain extraordinary amounts of selenium — but the content varies 10-fold depending on where they were grown. Consuming 1-2 nuts per day provides adequate selenium; consuming large amounts daily risks toxicity.
Animal foods vs. plant foods	Animal foods more reliable	Animals concentrate selenium from their feed, making meat, fish, and eggs more reliable selenium sources than plant foods in low-selenium soil regions
Selenium toxicity — selenosis	Upper limit is relatively close to requirement	The margin between adequate and toxic selenium intake is narrower than for most minerals. Chronic high intake (from supplements or high-selenium foods like certain seaweeds) causes hair loss, nail brittleness, neurological symptoms, and a characteristic garlic odour on the breath.

At-Risk Group	Core Reason	Key Signs or Consequences
Populations in low-selenium soil regions (parts of China, New Zealand, Finland historically, parts of Africa)	Soil selenium determines food selenium; no amount of dietary variety compensates if all local foods are grown in selenium-deficient soil	Keshan disease (selenium-deficient cardiomyopathy — heart failure); Kashin-Beck disease (osteoarthropathy); increased cancer risk
People with severe malabsorption or on long-term parenteral nutrition without selenium	Cannot absorb dietary selenium; parenteral nutrition not supplemented with selenium depletes stores over months	Cardiomyopathy; muscle weakness; immune dysfunction
Pregnant and lactating women in low-selenium areas	Increased demand during pregnancy and lactation in a population already at baseline risk	Impaired foetal antioxidant capacity; possible contribution to pregnancy complications

PRACTICE

The clinical lesson about selenium is restraint as much as adequacy. Unlike iron or zinc, where the primary concern is deficiency, selenium toxicity is a genuine clinical risk with supplementation. Recommending Brazil nuts, mixed seafood, and whole grains from varied geographic sources is safer than prescribing selenium supplements in populations without confirmed deficiency.

PART THREE — Phytonutrients: The Science of Protective Plant Compounds

Phytonutrients — also called phytochemicals or bioactive plant compounds — are not vitamins or minerals. They are not essential in the classical sense: a person will not develop a specific deficiency disease without them. But they are not nutritionally neutral either. Decades of epidemiological and mechanistic research demonstrate that populations eating diets rich in diverse plant foods have substantially lower rates of cardiovascular disease, several cancers, type 2 diabetes, and neurodegenerative disease — and that these protective effects are only partly explained by the vitamins and minerals in those plants. The remaining protection comes from the phytonutrients.

CONNECT

The most important thing to understand about phytonutrients is that they do not work as isolated compounds. The protective effect of a tomato cannot be replicated by a lycopene capsule. The benefit of broccoli is not simply its sulforaphane content. Whole food dietary patterns — where hundreds of phytonutrients interact synergistically — consistently outperform single-compound supplementation in clinical trials. This is why the dietary message always leads with food patterns, not supplements.

Polyphenols — The Largest and Most Diverse Family

Flavonoids, Phenolic Acids, Stilbenes & Lignans

What Are They and Where Are They Found?

Polyphenols are characterized by multiple phenol rings in their chemical structure. There are over 8,000 identified structures, making this the largest class of phytonutrients. They are responsible for much of the colour, bitterness, and astringency of plant foods — and their functional diversity is as large as their structural diversity.

Polyphenol Family		Key Examples	Primary Food Sources	Evidence-Based Health Association
Flavonoids Flavonols	—	Quercetin, kaempferol	Onions, kale, broccoli, apples, berries, tea	Anti-inflammatory; associated with reduced cardiovascular disease risk and improved lung function in observational studies
Flavonoids Anthocyanins	—	Cyanidin, malvidin	Berries (blueberries highest), red/purple grapes, red cabbage, aubergine	Blood pressure reduction; improved vascular function; reduced cognitive decline — strongest evidence among flavonoids for cardiovascular benefit
Flavonoids Isoflavones	—	Genistein, daidzein	Soybeans, edamame, tofu, tempeh	Weak oestrogen-like activity — associated with reduced menopausal symptoms in some women; evidence

			on breast cancer risk is mixed and population-dependent
Flavonoids — Flavan-3-ols	Epicatechin, EGCG	Green tea (richest source), cocoa/dark chocolate, grapes	Improved endothelial function; blood pressure reduction; cognitive support — one of the most studied polyphenol classes
Phenolic acids	Chlorogenic acid	Coffee (the largest single source of polyphenols in Western diets), berries, stone fruits	Associated with reduced type 2 diabetes risk; antioxidant and anti-inflammatory properties
Stilbenes	Resveratrol	Red grape skins, red wine, peanuts	Activates SIRT1 — a longevity-associated protein; cardiovascular protection in laboratory studies; human clinical evidence more limited
Lignans	Secoisolariciresinol	Flaxseeds (richest source), whole grains, sesame seeds	Converted by gut bacteria to enterolactone — weakly oestrogenic; associated with reduced breast cancer risk in postmenopausal women

How Do Polyphenols Protect Health?

Polyphenols do not work through a single mechanism. Their protective effects operate through multiple, overlapping pathways — which is partly why isolated supplements fail to replicate the benefit of whole foods containing these compounds.

Mechanism	What It Means in Practice	Example
Antioxidant activity	Polyphenols neutralize free radicals directly and — more importantly — activate the body's own antioxidant enzyme production (via the Nrf2 pathway)	Quercetin activates Nrf2, switching on the genes that produce superoxide dismutase, catalase, and glutathione peroxidase — the body's own antioxidant machinery
Anti-inflammatory signaling	Polyphenols inhibit the NF-κB pathway — the master switch for inflammatory gene expression — reducing production of pro-inflammatory cytokines	Curcumin (from turmeric), EGCG (from green tea), and quercetin all inhibit NF-κB; chronic low-grade inflammation is reduced with consistent polyphenol-rich diets
Gut microbiome modulation	Many polyphenols reach the colon intact and serve as food for beneficial bacteria — acting as prebiotics; gut bacteria also transform polyphenols into more bioactive metabolites	Ellagitannins (from pomegranates) are converted by gut bacteria to urolithins — compounds with anti-inflammatory and anti-cancer properties not present in the original food
Epigenetic regulation	Some polyphenols modify gene expression by altering histone acetylation and DNA methylation — influencing which genes are active without changing the DNA sequence itself	Sulforaphane inhibits HDAC enzymes, reactivating tumour-suppressor genes that have been silenced in cancer cells

Carotenoids Beyond Provitamin A

Lycopene, Lutein, Zeaxanthin — Eye Health and Cancer Prevention

What Are They and What Do They Do?

Carotenoids are fat-soluble yellow, orange, and red pigments in plants. Some — like beta-carotene — serve as vitamin A precursors and were covered in Lecture 1. The non-provitamin A carotenoids discussed here do not convert to vitamin A; their health roles are independent and are related to their antioxidant properties and selective tissue accumulation.

Carotenoid	Primary Sources	Where It Accumulates	Evidence-Based Role
Lycopene	Cooked tomatoes, tomato paste, watermelon, pink grapefruit	Prostate, skin, liver	Epidemiological association with reduced prostate cancer risk; most potent singlet oxygen quencher among common carotenoids. Bioavailability dramatically higher from cooked/processed tomatoes than raw — heat breaks down cell walls and releases lycopene.
Lutein & Zeaxanthin	Kale, spinach, corn, egg yolk, orange peppers	Retinal macula of the eye	The only carotenoids selectively accumulated in the macula, where they act as blue-light filters and antioxidants. Strong evidence for reducing progression of age-related macular degeneration (AMD) — one of the leading causes of blindness in older adults.
Astaxanthin	Salmon, shrimp, krill (the organisms that give these their pink colour)	Cell membranes throughout body	The most potent antioxidant carotenoid; crosses the blood-brain barrier; emerging evidence for reducing exercise-induced oxidative damage and inflammatory markers
Beta-cryptoxanthin	Oranges, mandarins, papayas, red capsicum	Lungs, bone	Provitamin A activity plus antioxidant role; associated with reduced lung cancer risk in smokers in observational studies; emerging evidence for bone health

WHY?

Lutein and zeaxanthin represent one of the strongest evidence-based cases for specific phytonutrients in disease prevention. The AREDS2 trial — a large randomized clinical trial — demonstrated that supplementation with lutein and zeaxanthin (10mg and 2mg respectively) reduced progression to advanced AMD by approximately 25% in people with intermediate AMD. This is one of the few phytonutrient interventions where the evidence moves beyond epidemiological association to randomized trial evidence.

PRACTICE

The lycopene bioavailability principle has an immediate dietary counselling application: recommending cooked tomatoes, tomato paste, or tomato-based sauces is more effective for lycopene delivery than raw tomatoes. Adding a small amount of olive oil or another fat source further improves absorption of this fat-soluble carotenoid. This is a simple, affordable, and culturally accessible recommendation for populations across Africa and the Middle East where tomatoes are dietary staples.

Glucosinolates & Isothiocyanates

The Cruciferous Vegetable Compounds — Cancer Prevention Evidence

What Are They and How Do They Work?

Glucosinolates are sulphur-containing compounds found exclusively in cruciferous vegetables — broccoli, cauliflower, cabbage, Brussels sprouts, kale, arugula, watercress, and radish. When these vegetables are chopped, chewed, or damaged, an enzyme called myrosinase is activated and converts glucosinolates into isothiocyanates (ITCs) — the biologically active compounds. This is a plant defence system against insects and pathogens that, in humans, produces a range of cancer-protective effects.

Key Compound	Primary Source	Main Mechanism of Protection
Sulforaphane (from glucoraphanin)	Broccoli, especially sprouts (10-100x more concentrated than mature broccoli)	Activates Nrf2 — the master switch for the body's detoxification and antioxidant enzyme systems. Also inhibits HDAC enzymes, reactivating silenced tumour-suppressor genes. Has completed Phase I/II clinical trials for cancer prevention in prostate, breast, lung, and colorectal cancer.
Indole-3-carbinol (I3C) and DIM	All cruciferous vegetables	Modifies oestrogen metabolism — shifting it toward less active forms. Associated with reduced risk of hormone-dependent cancers (breast, endometrial) in observational studies; also has direct anti-proliferative effects on cancer cell lines.
Phenethyl isothiocyanate (PEITC)	Watercress, radish	Inhibits enzymes that activate tobacco carcinogens; Phase II clinical data suggests reduced DNA damage in tobacco-exposed individuals

CAUTION

Myrosinase — the enzyme that converts glucosinolates to the active isothiocyanates — is heat-labile. Boiling cruciferous vegetables inactivates myrosinase and dramatically reduces isothiocyanate formation. The protective compounds are present in the raw vegetable, but their conversion requires either eating the vegetable raw, lightly steaming, or microwaving (less myrosinase destruction than boiling). Gut bacteria also possess myrosinase activity, providing some backup conversion even from cooked vegetables.

PRACTICE

The dietary counselling recommendation for cruciferous vegetables has a preparation qualifier: light steaming, microwaving, or raw consumption preserves far more cancer-protective ITCs than boiling. Chopping or chewing activates myrosinase before cooking somewhat mitigates the effect of mild heat. Recommending 3-5 servings per week of varied cruciferous vegetables, prepared with minimal water and heat, is a practical and evidence-grounded dietary goal.

Organosulfur Compounds — Allium Vegetables

Garlic, Onions, Leeks and the Cardiovascular Evidence

What Are They and What Do They Do?

Allium vegetables — garlic, onions, leeks, shallots, chives — contain unique sulphur-containing compounds that are released when the vegetable is cut, crushed, or chewed. In garlic, the compound alliin is converted by the enzyme alliinase to allicin — which is responsible for the characteristic odour and many of the biological effects. Allicin is unstable and rapidly transforms into a range of other active compounds including diallyl disulphide and diallyl trisulphide, which are the forms actually absorbed and active in the body.

Evidence-Based Effect	Strength of Evidence	Dietary Relevance
Modest reduction in LDL cholesterol and total cholesterol	Systematic review and meta-analysis support — effect is real but modest (approximately 5-10% reduction)	Clinically meaningful as part of a broader dietary pattern; not a substitute for lipid-lowering medication in high-risk individuals
Blood pressure reduction	Multiple meta-analyses demonstrate modest but significant reductions in both systolic and diastolic BP	Effect comparable to some low-dose antihypertensive medications in mildly hypertensive individuals; strongest with aged garlic extract or raw garlic
Inhibition of platelet aggregation	Laboratory and some human studies support anti-thrombotic effect	May contribute to cardiovascular protection but also a caution in people on anticoagulant therapy — garlic supplements can potentiate warfarin effects

Antimicrobial activity	Allicin has demonstrated activity against H. pylori, S. aureus, Candida, and E. coli in laboratory studies	Clinical relevance for H. pylori (associated with gastric cancer) is promising but not yet sufficiently established for clinical recommendation
Immune modulation	Some evidence that garlic consumption reduces severity and duration of upper respiratory infections	Consistent with the anti-inflammatory and immune-stimulating properties of organosulfur compounds

CONTEXT

Garlic and onion are central ingredients in Sudanese and broader African and Middle Eastern cuisine — present in almost every savory dish. This is an example where culturally embedded traditional dietary patterns may be delivering health benefits that are only now being quantified by science. The dietary counselling implication is reinforcement — not introduction — of an existing practice.

The Whole-Food Principle — Why Pattern Beats Supplement

Throughout this lecture, a consistent pattern has emerged: isolated mineral or phytonutrient supplements rarely replicate the benefits of eating the whole food that contains them. This is not an accident — it reflects several fundamental biological realities that every dietitian should understand and communicate.

Why Whole Food Outperforms Supplements	The Biological Explanation	The Practical Implication
Synergistic interactions between nutrients	In whole food, hundreds of nutrients, phytonutrients, fibre, and mineral cofactors interact in ways that no supplement can replicate. Vitamin C in an orange enhances iron absorption from the same meal; the fat in an avocado enhances carotenoid absorption from the same salad; the fibre in a legume modifies how its minerals are absorbed.	Dietary pattern counselling — diverse, minimally processed, whole-food diets — is the evidence base, not individual nutrient supplementation
Gut microbiome transformation of phytonutrients	Many phytonutrients are not active in the form they are consumed. They reach the colon and are converted by gut bacteria into the biologically active compounds. An individual's ability to benefit from certain phytonutrients depends on their microbiome composition — which supplements bypass.	Protecting and cultivating gut microbiome diversity (through fibre, fermented foods, dietary variety) is as important as the phytonutrient intake itself
Hormesis — the dose matters	Many protective phytonutrients work through mild cellular stress that activates protective responses. At high supplemental doses, this hormetic effect may be lost or reversed. Sulforaphane at low food-derived doses activates Nrf2; at very high doses it becomes cytotoxic.	Emphasize dietary variety over high-dose single-compound supplements; the dose delivered by food is calibrated by millions of years of co-evolution

Bioavailability is context-dependent	The same mineral or phytonutrient is absorbed differently depending on what surrounds it in the food matrix. Lycopene in a tomato sauce with olive oil is absorbed far better than lycopene in a capsule; iron in a meal with vitamin C is absorbed far better than iron supplemented separately from food.	Dietary counselling must address not just what to eat but how to combine, prepare, and time foods
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Clinical Scenario: A Comprehensive Nutritional Assessment

- Amira is a 34-year-old primary school teacher in a peri-urban area. She is vegetarian and rarely eats meat or fish. She drinks 4-5 cups of tea daily — usually with meals. Her diet is based on sorghum flatbread, lentils, broad beans, spinach, and tomatoes. She is in her second trimester of pregnancy. She reports fatigue, breathlessness on exertion, and brittle nails. Her haemoglobin is 9.2 g/dL.
- Question 1: Identify all the factors in Amira's dietary pattern and lifestyle that are compromising her iron status. For each factor, explain the specific mechanism.
- Question 2: Her diet contains iron-rich foods (lentils, broad beans). Why is she still iron deficient — and what would you change about how, when, and with what she eats these foods?
- Question 3: Beyond iron, what other mineral and vitamin deficiencies might Amira be at risk of — given her pregnancy, vegetarian diet, and food choices? Justify each.
- Question 4: Her GP suggests she simply needs an iron supplement. What would you add to this recommendation, and why?
- Question 5: Which phytonutrients are already present in Amira's diet — and what additional plant foods would you recommend to strengthen the protective plant compound component of her diet?

Critical Thinking Questions

- A patient tells you she takes a multivitamin and mineral supplement every day and believes this provides her nutritional needs. She therefore does not worry about eating fruits, vegetables, or whole grains. Using the principles from this lecture, explain why this reasoning is nutritionally flawed — and do so in language that would be meaningful to a patient, not a scientist.
- In many African and Middle Eastern communities, tea is consumed with every meal as a deeply embedded cultural practice. You know that tea tannins significantly reduce iron absorption. How do you approach this in dietary counselling — and what is the evidence-based recommendation that respects both the nutritional concern and the cultural context?
- Phytonutrient research is one of the fastest-growing areas in nutrition science, with new compounds and mechanisms identified regularly. At the same time, many supplement companies make strong health claims for isolated phytonutrient supplements. As a practicing dietitian, how do you evaluate the strength of evidence for a new phytonutrient claim — and what criteria would you use before recommending a phytonutrient supplement to a patient?

Lecture Summary — Key Takeaways for Dietetic Practice

- Bioavailability is the central concept of mineral nutrition: what the body absorbs from food is often far less than what the food contains. The source of the mineral, food preparation method, co-consumed foods (enhancers and inhibitors), and the person's physiological state all determine actual mineral status.
- Iron: the most common nutritional deficiency globally. Haem iron (animal foods) is absorbed 15-35%; non-haem iron (plant foods) only 2-20% and is strongly inhibited by tea, coffee, phytate, and calcium. Vitamin C and meat-fish-poultry factor are the primary dietary enhancers. Brain effects precede anaemia — do not wait for low haemoglobin to act.
- Zinc: no storage depot — deficiency develops rapidly. Phytate is the dominant inhibitor; animal protein enhances absorption. Growth faltering in children is the most sensitive indicator. Fermentation and soaking reduce phytate and improve bioavailability from plant foods.
- Calcium: 99% structural, 1% signaling — the body sacrifices bone calcium to maintain blood calcium, so serum calcium is not a status indicator. Vitamin D status is the most important determinant of absorption efficiency. Oxalate in spinach renders its calcium almost unusable; low-oxalate greens (kale, broccoli) are good plant calcium sources.
- Iodine: required solely for thyroid hormone synthesis. Deficiency during pregnancy causes irreversible brain damage — the world's leading preventable cause of intellectual disability. Goitrogens in cassava worsen deficiency. Universal salt iodization is the primary prevention strategy.
- Phytonutrients — the protective plant compound principle: polyphenols, carotenoids, glucosinolates, and organosulfur compounds protect health through antioxidant, anti-inflammatory, epigenetic, and microbiome-mediated mechanisms. Whole food dietary patterns consistently outperform isolated supplements — the matrix, synergy, and microbiome transformation of phytonutrients cannot be replicated in a capsule.

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Phytochemicals

A Clinical Reasoning Approach: Food Sources, Mechanisms of Protection & Evidence-Based Health Benefits

Focus: Why specific plant foods protect health — and how to translate that into practical dietary recommendations

What Are Phytochemicals — and Why Do They Matter?

Phytochemicals are biologically active compounds found exclusively in plants. They are not vitamins or minerals — the body does not require them to prevent a classical deficiency disease. But they are far from nutritionally neutral. Decades of research consistently show that populations eating diverse, plant-rich diets have substantially lower rates of cardiovascular disease, several cancers, type 2 diabetes, and neurodegenerative disease — and that these protective effects cannot be fully explained by the vitamins, minerals, and fibre in those plants alone. The protection that remains after accounting for classical nutrients is largely attributable to phytochemicals.

WHY?

Plants produce phytochemicals for their own purposes — as pigments to attract pollinators, as bitter compounds to deter herbivores, as antimicrobials to prevent infection, and as UV screens to prevent radiation damage. When humans eat these plants, many of these defesce and signaling compounds activate protective pathways in human cells that overlap with our own needs for disease prevention. This is why 'eat the rainbow' is not just a slogan — different plant colours reflect different phytochemical families with different protective mechanisms.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain what phytochemicals are, how they differ from classical nutrients, and why they are essential to a complete understanding of food and health
- Identify the major families of phytochemicals, their primary food sources, and the factors that affect how much the body can absorb and use
- Describe the key mechanisms by which phytochemicals protect health — focusing on the pathways relevant to cardiovascular disease, cancer, and type 2 diabetes
- Explain the role of the gut microbiome in transforming phytochemicals and why individual response to plant foods varies

- Distinguish between the strength of evidence for different phytochemicals — from strong epidemiological and trial evidence to promising but preliminary findings
- Translate phytochemical science into practical, culturally relevant dietary counselling recommendations

PART ONE — How Phytochemicals Work: The Four Key Mechanisms

Before examining individual phytochemical families, it is essential to understand how they protect health. Most phytochemicals do not work through a single mechanism — they activate multiple, overlapping pathways simultaneously. Four mechanisms are most clinically important and appear repeatedly across different phytochemical families.

Mechanism	What It Means in Plain Terms	Which Diseases It Protects Against	Example Phytochemicals
Activating the Nrf2 pathway (the cell's own defence gene switch)	Nrf2 is a master switch inside cells that, when activated, turns on over 200 genes — producing antioxidant enzymes, detoxification proteins, and anti-inflammatory molecules. Phytochemicals activate this switch, making the cell more resistant to oxidative damage and carcinogens.	Cancer prevention (Phase II detoxification enzymes neutralize carcinogens before they damage DNA); cardiovascular protection (endothelial defence); reduces oxidative stress in diabetes	Sulforaphane (broccoli sprouts — most potent known activator), curcumin, quercetin, EGCG (green tea), allicin (garlic), lycopene
Suppressing NF-kB (the inflammation gene switch)	NF-kB is the master switch for inflammation — when chronically activated, it produces a continuous stream of inflammatory molecules that damage blood vessels, promote cancer growth, and worsen insulin resistance. Many phytochemicals block this switch, reducing chronic low-grade inflammation.	Cardiovascular disease (arterial inflammation is central to atherosclerosis); cancer promotion (NF-kB keeps damaged cells alive); T2DM (inflammatory cytokines worsen insulin resistance); arthritis, IBD	Curcumin, quercetin, resveratrol, EGCG, anthocyanins, allicin, omega-3 fatty acids
Activating AMPK (the cellular energy sensor)	AMPK is a molecular sensor that detects when cells need more energy. When activated, it switches the cell into 'energy conservation mode' — improving glucose uptake, reducing fat synthesis, improving mitochondrial function, and mimicking some effects of caloric restriction and exercise.	Type 2 diabetes prevention and management (improves insulin sensitivity); cardiovascular disease (reduces lipid synthesis); obesity (reduces fat accumulation); cancer (AMPK activation suppresses mTOR, which cancer cells need for growth)	Berberine (most potent AMPK activator among phytochemicals; comparable to metformin), resveratrol, EGCG, quercetin, chlorogenic acid (coffee)
Gut microbiome transformation (the hidden converter)	Many phytochemicals cannot be absorbed in the small intestine — they arrive in the colon intact, where gut bacteria convert them into smaller,	All conditions benefited by phytochemicals — but the magnitude of benefit varies	Ellagitannins (pomegranate, walnuts) → urolithins; isoflavones (soy) →

	more bioavailable, and often more potent bioactive compounds. The individual's microbiome composition determines how effectively this conversion occurs.	between individuals based on microbiome composition	equol; lignans (flaxseed) → enterolactone; chlorogenic acid (coffee) → dihydrocaffeic acid
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CONNECT

These four mechanisms explain a pattern that appears throughout this lecture: phytochemicals that activate Nrf2 tend to also suppress NF-κB (because Nrf2 activation produces molecules that block NF-κB); phytochemicals that activate AMPK tend to also reduce oxidative stress (because AMPK improves mitochondrial efficiency). This is why plant foods with diverse phytochemical content are more protective than any single isolated compound — multiple pathways are activated simultaneously.

PART TWO — The Major Phytochemical Families

Phytochemicals are classified by their chemical structure into several major families. Each family has characteristic food sources, bioavailability characteristics, and health effects. The most clinically important are covered in order of evidence strength.

Polyphenols — The Largest and Most Studied Family

Flavonoids, Phenolic Acids, Stilbenes & Lignans

The Flavonoid Sub-Family — Found in Almost Every Plant Food

Flavonoids are the most abundant polyphenols in the human diet — present in virtually all fruits, vegetables, legumes, tea, coffee, wine, and cocoa. They share a basic chemical structure but divide into six sub-classes with distinct food sources and health effects.

Flavonoid Sub-class	Primary Food Sources	Key Health Effect	Strength of Evidence
Flavonols (Quercetin, Kaempferol)	Onions (especially outer rings and red varieties), kale, broccoli, apples (skin), capers, tea, red wine	Blood pressure reduction; anti-inflammatory (NF-κB suppression); anti-atherosclerotic; inhibits carcinogen-activating enzymes (CYP1A1); chelates free iron (preventing Fenton reaction)	Strong — meta-analysis of >30 RCTs: quercetin significantly reduces systolic (-3.1 mmHg) and diastolic (-2.2 mmHg) BP, reduces CRP. Dietary quercetin inversely associated with CVD mortality in large

			cohorts (EPIC, Nurses' Health Study).
Flavan-3-ols (Catechins, EGCG)	Green tea (richest source: 50-300mg EGCG/cup), dark chocolate/cocoa (epicatechin), red wine, apples, grapes	Endothelial function improvement; blood pressure reduction; LDL-C reduction; neuroprotection; anti-cancer (epigenetic mechanisms — inhibits DNMT, reactivating silenced tumour-suppressor genes)	Strong — COSMOS trial: cocoa flavanol 600mg/day → 21% reduction in CVD mortality over 3.6 years. Meta-analyses: green tea → ~28% reduction in T2DM incidence; improved FMD (endothelial function marker) in 22 RCTs.
Anthocyanins (Cyanidin, Malvidin)	Blueberries, blackberries, raspberries, cherries, elderberries, red/purple grapes, red cabbage, purple corn	Endothelial protection; blood pressure reduction; improved insulin sensitivity; anti-inflammatory; neuroprotective; cross blood-brain barrier	Strong for CVD — blueberry RCTs: 1 cup/day for 6 weeks significantly improves flow-mediated dilation in metabolic syndrome. Anthocyanin intake inversely associated with T2DM risk (RR 0.85) in prospective cohorts. Elderberry meta-analysis: ~2 day reduction in cold/flu duration.
Flavanones (Hesperidin, Naringenin)	Citrus fruits — oranges (hesperidin), grapefruit (naringenin, naringin); concentrated in peel/pith, partially lost in juicing	Anti-inflammatory; improves lipid profile; grapefruit naringenin inhibits CYP3A4 in the intestine (significant drug interactions)	Moderate — RCTs show improvement in lipid profiles and inflammatory markers. Critically important for drug interactions: grapefruit juice inhibits CYP3A4 irreversibly → markedly increases blood levels of statins, cyclosporine, amlodipine, midazolam — interaction persists 24-72 hours after consumption.
Isoflavones (Genistein, Daidzein)	Soybeans, edamame, tofu, tempeh (highest bioavailability from fermented forms), miso, soy milk	Weak oestrogen-like activity (SERM) — beneficial for menopausal symptoms; protective against hormone-sensitive cancers in populations with lifelong exposure;	Moderate/context-dependent — Asian cohort studies show inverse association with breast and prostate cancer; Western supplementation data

		modulated by gut microbiome (equol production)	mixed. ~25% reduction in hot flush frequency in RCTs. Safe for breast cancer survivors at food levels (WHO, WCRF consensus).
Stilbenes (Resveratrol)	Red grape skins, red wine (small amounts), peanuts, mulberries, Japanese knotweed (supplement source)	SIRT1 activation → mimics effects of caloric restriction; anti-inflammatory (NF-κB); cardioprotective in laboratory and some human studies	Mixed — compelling mechanistic data, limited clinical translation due to rapid metabolism (half-life <30 min). Some RCT benefit in T2DM and NAFLD; cardiovascular outcome trials neutral. Bioavailability-enhanced forms under development.

CAUTION

Grapefruit-drug interaction: This is a genuine, clinically significant safety issue that dietitians must know. Furanocoumarins in grapefruit (not naringenin itself) irreversibly inhibit intestinal CYP3A4, markedly increasing the bioavailability of CYP3A4-metabolised drugs. The interaction lasts 24-72 hours. Affected drugs include: simvastatin/atorvastatin (statin toxicity risk), cyclosporine (transplant rejection risk if dose appears too low), amlodipine, midazolam, tacrolimus. One glass of grapefruit juice can cause a clinically significant drug interaction.

Phenolic Acids — The Most Abundant Polyphenols in Most Diets

While flavonoids receive the most research attention, phenolic acids — particularly chlorogenic acids from coffee — are actually the most consumed polyphenols in Western and many African diets. A regular coffee drinker may consume over 1 gram of chlorogenic acid per day — more than any other single phytochemical category.

Phenolic Acid Source	Key Compounds	Primary Mechanisms	Clinical Evidence
Coffee (by far the largest source)	Chlorogenic acids (CQAs) — 70-350mg per cup; also diterpenes (cafestol, kahweol) in unfiltered coffee	Inhibits alpha-glucosidase and alpha-amylase (reduces postprandial glucose); inhibits hepatic glucose-6-phosphatase (reduces fasting glucose output); activates AMPK; Nrf2 activation; gut microbiome modulation	Meta-analysis (28 cohort studies, >1 million participants): 3-4 cups/day → 25-30% reduction in T2DM risk. Both caffeinated and decaffeinated coffee are protective — implicating chlorogenic acids, not caffeine. EPIC cohort: ~15% reduction in

			all-cause mortality with moderate coffee intake. Inverse associations with Parkinson's disease, Alzheimer's, liver cirrhosis, and hepatocellular carcinoma.
Whole grains, especially oats and rye	Ferulic acid (bound to cell walls; partially released by gut bacteria); avenanthramides (oats only)	Ferulic acid: antioxidant, anti-inflammatory, anti-cancer (inhibits carcinogen-activating CYPs); avenanthramides: anti-inflammatory, anti-itch, unique to oats	Dietary whole grain intake inversely associated with T2DM, CVD, and colorectal cancer across major cohort studies. Ferulic acid bioavailability from whole grains is low but enhanced by fermentation and cooking.
Berries, stone fruits	Ellagic acid, protocatechuic acid	Ellagic acid: precursor to ellagitannins which gut bacteria convert to urolithins — more bioactive than ellagic acid itself	Strawberries, raspberries, pomegranates — ellagic acid content high; but the key bioactive compounds are the urolithins formed in the colon. Individual variation is enormous (see gut microbiome section).

CONTEXT

Coffee is the world's most widely consumed phytochemical-rich beverage — including in Sudan, where it is deeply embedded in cultural practice (the jabana coffee ceremony, qahwa). The evidence consistently showing protective effects of moderate coffee consumption (3-4 cups/day) against diabetes, liver disease, and neurodegenerative disease is one of the most robust findings in nutritional epidemiology. For patients who already drink coffee, this is a dietary pattern to reinforce — not restrict.

Lignans — The Fermented-Food Phytochemicals

Lignans are phytochemicals found primarily in seeds and whole grains that require gut bacterial transformation to become biologically active. The parent compounds in food (secoisolariciresinol in flaxseed) are converted by specific gut bacteria into enterolactone and enterodiol — the active mammalian lignans with weak oestrogenic and anti-cancer activity.

Lignan Source	Amount	Health Effect	Key Point
Flaxseeds (richest source by far)	~300mg SDG per 100g — orders of magnitude more than other foods	Breast cancer risk reduction (postmenopausal); improved lipid profile; blood glucose control; antioxidant	Ground flaxseed is needed — whole seeds pass undigested. One tablespoon ground flaxseed

			daily provides meaningful lignan exposure. Also provides ALA (plant omega-3) and soluble fibre — a triple benefit.
Sesame seeds	High in sesamin and sesamol — different lignan sub-types	Blood pressure reduction; antioxidant; anti-inflammatory	Sesame and sesame oil are widely used in Sudanese and Middle Eastern cooking — a culturally relevant lignan source. Sesame lignans have demonstrated antihypertensive effects in RCTs.
Whole grains (rye, barley, oats)	Lower amounts but consistently present	Contributes to total lignan intake in whole grain-eating populations	The shift from whole grain to refined grain in dietary transitions removes this lignan source — one of many micronutrient losses associated with food processing.

CONNECT

*The lignan story perfectly illustrates the microbiome-dependence of phytochemical action. Enterolactone production from flaxseed lignans requires specific bacteria (*Lactonifactor longoviformis*, *Blautia producta*). People with low microbiome diversity — from antibiotic overuse, low dietary fibre, or ultra-processed food-dominant diets — produce far less enterolactone from the same amount of flaxseed. This is why dietary fibre and fermented food intake are not separate from phytochemical benefit — they are prerequisites for it.*

Glucosinolates & Isothiocyanates

The Cruciferous Vegetable Compounds — Broccoli, Cabbage & Watercress

The Mechanism: Plant Defense as Human Medicine

Glucosinolates are sulphur-containing compounds produced by all cruciferous vegetables as a defense against insects — they taste bitter and are toxic to many pests. When cruciferous vegetables are cut, chewed, or damaged, an enzyme called myrosinase (stored separately in the plant) contacts the glucosinolates and converts them into isothiocyanates (ITCs) — the biologically active compounds. In humans, these ITCs are among the most potent known activators of Nrf2 and the body's detoxification system.

WHY?

The myrosinase-glucosinolate system is the plant equivalent of a binary chemical weapon — harmless when the plant is intact, activated only when the plant is damaged. For humans eating cruciferous vegetables, the practical implication is critical: myrosinase is heat-sensitive. Boiling cruciferous vegetables for extended periods destroys myrosinase and dramatically reduces ITC formation. How you cook the vegetable determines how much of the cancer-protective compound you actually receive.

Cruciferous Family	Vegetable	Key Glucosinolate / ITC Produced	Primary Protective Mechanism	Cooking Guidance
	Broccoli, especially broccoli sprouts (sprouts contain 10-100x more)	Glucoraphanin → Sulforaphane (SFN) Most studied and most potent dietary Nrf2 activator known	SFN modifies Keap1 (the Nrf2 'keeper') → Nrf2 switches on Phase II detoxification enzymes (GST, NQO1, HO-1, GCL) → carcinogens neutralized before DNA damage; also inhibits HDAC (reactivates silenced tumour-suppressor genes); anti-H. pylori activity; reduces hepatic glucose production in T2DM	Raw or lightly steamed. If cooking, add raw mustard seed powder or daikon radish (external myrosinase source) to cooked broccoli. Broccoli sprouts (30-50g) used in clinical trials — the most potent dietary source.
	All cruciferous vegetables (cabbage, Brussels sprouts, kale, cauliflower)	Glucobrassicin → Indole-3-carbinol (I3C) → DIM (diindolylmethane) in the stomach	Modifies oestrogen metabolism — shifts toward less active oestrogen forms (2-OH vs 16α-OH); weak oestrogen receptor antagonist; inhibits CDK2/4 (cell cycle arrest); anti-angiogenic	Standard cooking is acceptable — indoles are heat-stable (unlike glucoraphanin). Include multiple cruciferous types weekly for ITC diversity.

Watercress, garden cress, radish	Gluconasturtiin → PEITC (phenethyl isothiocyanate)	Inhibits CYP2E1 and CYP2A6 — the liver enzymes that activate tobacco carcinogens into DNA-damaging forms; Phase 2 clinical trial demonstrated single watercress meal significantly reduced tobacco carcinogen metabolites in smokers	Best consumed raw — classic watercress salad is optimal delivery. One of the few phytochemicals with demonstrated carcinogen-blocking activity in human clinical trials.
Mustard seeds, horseradish, wasabi	Sinigrin → Allyl isothiocyanate (AITC)	Antimicrobial (including against food-borne pathogens); anti-cancer cell migration and invasion; activates TRPA1 receptor (the 'heat' sensation of wasabi/mustard)	Traditional condiments that deliver bioactive ITCs — culturally relevant in many cuisines where mustard is used in cooking and salad dressings.

EVIDENCE

Sulforaphane clinical evidence: Broccoli sprout extract reduced aflatoxin-DNA adducts (a marker of liver cancer risk) in a randomized trial in China. SFN (200 micromoles/day) reduced PSA velocity in men with recurrent prostate cancer. Broccoli sprout extract significantly reduced fasting blood glucose and HbA1c vs placebo over 12 weeks in T2DM patients. These are Phase II clinical trial results — not just laboratory data.

PRACTICE

The practical counselling message for cruciferous vegetables has two parts: (1) Include them regularly — at least 3-5 servings per week; the epidemiological evidence for cancer protection is consistent. (2) Prepare them to maximize ITC delivery — steam or microwave rather than boil; eat some raw; add mustard to cooked broccoli. A patient who eats boiled Brussels sprouts every day may receive far less sulforaphane than one who eats raw broccoli florets twice per week.

Organosulfur Compounds from Allium Vegetables

Garlic, Onions, Leeks — The Cardiovascular Phytochemicals

The Allicin System — Another Binary Mechanism

Like glucosinolates in cruciferous vegetables, the bioactive compounds in allium vegetables are formed only when the plant is damaged. In garlic, alliin (an inactive sulphur-containing amino acid) contacts alliinase (the activating enzyme) when the clove is cut or crushed — producing allicin, the compound responsible for garlic's characteristic odour and most of its biological activity. Allicin is unstable and rapidly transforms into other active sulphur compounds (diallyl disulphide, diallyl trisulphide, ajoene) that are absorbed and active in the body.

Allium Vegetable	Key Phytochemicals	Primary Health Effects	Preparation Note
Garlic	Allicin (from crushing/chopping); DATS (diallyl trisulphide — most potent cancer-cell apoptosis inducer among garlic compounds); S-allylcysteine (SAC — the stable, most bioavailable compound in aged garlic extract)	CVD: reduces LDL-C, total cholesterol, triglycerides, and blood pressure (39-RCT meta-analysis); antimicrobial including H. pylori; immune modulation; anti-cancer (HDAC inhibition, apoptosis induction); Nrf2 activation	Crush or mince and allow 10-minute rest before cooking — this maximizes allicin formation before heat destroys alliinase. Aged garlic extract (AGE/Kyolic) provides standardized, stable SAC — the preferred supplemental form.
Onions	Quercetin (highest concentration in outer rings and red/yellow varieties); fructooligosaccharides (FOS — prebiotic fibre); organosulfur compounds (less than garlic)	CVD protection (quercetin + organosulfur synergy); prebiotic effect (FOS → feeds Bifidobacterium); anti-platelet aggregation; anti-inflammatory	Quercetin is largely in the outer layers — avoid peeling too deeply. Red onions provide anthocyanins in addition to quercetin. Raw onions deliver more quercetin than cooked.
Leeks	Kaempferol (flavonol with anti-cancer properties in epidemiological studies); folate (64mcg/100g); vitamin K	Anti-cancer (kaempferol inversely associated with ovarian and lung cancer in cohort studies); folate contribution; vitamin K for coagulation and bone health	Mild enough to use raw in salads — reduces cooking-related phytochemical loss. Both the white bulb and green tops are nutritious.
Spring onions / Scallions	Quercetin, organosulfur compounds; vitamin K, vitamin C	Similar profile to onions with the added benefit of vitamin C and K from the green tops	The green tops should be included — they contain most of the vitamin K and additional polyphenols that are discarded if only the white part is used.

EVIDENCE	<i>Garlic supplementation meta-analysis (39 RCTs, n>2,600): significant reductions in total cholesterol (-17 mg/dL), LDL-C (-9 mg/dL), triglycerides (-11 mg/dL), and systolic blood pressure (-3.75 mmHg). Aged garlic extract (AGE) shows the most consistent cardiovascular evidence — standardized, odour-free, and bioavailable. Effect on blood pressure comparable to low-dose antihypertensive medication in mildly hypertensive individuals.</i>
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CONTEXT

Garlic and onion are central to Sudanese cuisine — present in virtually every savoury dish. This is a case where culturally embedded traditional dietary patterns are delivering measurable health benefits that science is only now quantifying. The counselling message is reinforcement: the way Sudanese cooking uses abundant garlic and onion as flavour bases is nutritionally protective. Discouraging their use in the name of 'modern healthy eating' would be counterproductive.

Carotenoids Beyond Provitamin A

Lycopene, Lutein, Zeaxanthin & Astaxanthin

What Makes Non-Provitamin A Carotenoids Different

Beta-carotene's role as a vitamin A precursor was covered in the fat-soluble vitamins lecture. The non-provitamin A carotenoids discussed here do not convert to vitamin A — their health roles are entirely independent, based on their antioxidant properties (especially singlet oxygen quenching) and their selective accumulation in specific tissues where protection is most needed.

Carotenoid	Primary Food Sources	Where It Concentrates in the Body	Evidence-Based Health Role
Lycopene	Cooked and processed tomatoes (tomato paste, canned tomatoes, tomato sauce — more bioavailable than raw); watermelon; pink grapefruit; guava	Prostate gland, skin, liver, adrenal glands — particularly high concentration in prostate tissue	Prospective cohort evidence: highest lycopene quartile → ~40% reduction in prostate cancer risk (Health Professionals Follow-up Study); effect strongest for advanced and lethal disease. Phase 2 RCT: lycopene 15mg/day reduced PSA, tumor proliferation index, and oxidative DNA damage pre-surgically. Cardioprotective — reduces LDL oxidation. Key point: cooking with fat dramatically increases bioavailability.
Lutein + Zeaxanthin	Kale (highest — 39mg/100g), spinach (12mg), collard greens, corn, egg yolk, orange peppers	Selectively accumulated in the retinal macula (the high-resolution central vision area) — the only carotenoids found there	AREDS2 RCT (gold standard evidence): lutein 10mg + zeaxanthin 2mg/day → 25% reduction in progression to advanced age-related macular degeneration (AMD). Replaced beta-carotene in the AREDS formula because beta-carotene increased lung cancer risk in smokers. Also accumulating in brain tissue — emerging cognitive data

			shows brain lutein correlates with processing speed and memory in older adults.
Astaxanthin	Wild salmon, krill, shrimp, microalgae (Haematococcus pluvialis — the commercial supplement source)	Cell membranes throughout the body; crosses the blood-brain barrier and blood-retinal barrier — penetrates tissues that most carotenoids cannot	10-100x more potent antioxidant than beta-carotene in laboratory measures. Reduces exercise-induced oxidative damage and inflammation in RCTs. Neuroprotective in preclinical models. Early trials in NAFLD and cognitive decline showing promise. Not currently a major dietary source for most populations — relevant primarily as a supplement consideration.
Beta-cryptoxanthin	Mandarins, tangerines, oranges, papayas, paprika, pumpkin	Lung tissue, joints	Both provitamin A activity (can convert to vitamin A) and independent antioxidant role. Inverse association with lung cancer (non-smoking-related mechanism), rheumatoid arthritis, and bone loss in prospective cohort studies. May have bone-protective effects independent of vitamin A.

WHY?

Lycopene's bioavailability story is the most important practical point in this section: raw tomatoes provide approximately 3mg lycopene per 100g with low bioavailability; tomato paste provides 45mg per 100g with much higher bioavailability because cooking breaks down cell walls and converts trans-lycopene to the more easily absorbed cis-isomer. Adding olive oil further increases absorption because lycopene is fat-soluble. A traditional Sudanese/Middle Eastern tomato-based sauce cooked in oil is actually a superior lycopene delivery vehicle to a raw tomato salad.

Phytosterols — The Cholesterol Competitors

Plant Compounds That Block Cholesterol Absorption

How Phytosterols Work

Phytosterols are structural components of plant cell membranes — the plant equivalent of cholesterol. Because their chemical structure is very similar to cholesterol, they compete with cholesterol for absorption in the intestine: when phytosterols are present, less cholesterol can be absorbed. This makes phytosterols unique among phytochemicals — they have a well-established, specifically approved health claim for LDL cholesterol reduction, supported by over 100 randomized controlled trials.

Phytosterol Source	Amount per Serving	Effective Dose for LDL Reduction	Clinical Evidence
Plant oils (wheat germ, sesame, corn, sunflower)	Significant amounts in unrefined oils; largely removed in refining	2g/day is the clinically effective dose — difficult to achieve from unfortified foods alone	Meta-analysis of >100 RCTs: 2g/day phytosterol esters → ~10% reduction in LDL-C. Effect is additive to statin therapy. FDA-approved health claim: 'Foods containing at least 0.65g of plant sterol esters per serving, eaten twice a day with meals, may reduce the risk of heart disease.' European Society of Cardiology: Class IIa recommendation.
Nuts (pistachios, almonds, walnuts)	~100-200mg per 30g serving	Would require 10+ servings of nuts to reach 2g — supplementary sources needed for therapeutic effect	Nuts provide phytosterols as part of a package with unsaturated fats, protein, fibre, and polyphenols — the combination likely more beneficial than phytosterols alone
Fortified foods (margarines, orange juice, yogurt)	Specifically formulated to deliver 1.0-1.5g per serving	2 servings daily achieves therapeutic dose reliably	Fortified margarines and dairy products are the primary clinical delivery vehicle. Note: high-dose phytosterols reduce carotenoid absorption — advise adequate carotenoid-rich food intake alongside phytosterol products.

PRACTICE	<i>Phytosterols are the most evidence-based phytochemical intervention for LDL reduction — with a level of evidence comparable to low-dose statin therapy for mild hypercholesterolaemia. For patients with LDL above target who decline or cannot tolerate statins, phytosterol-enriched foods (2g/day) are a first-line dietary intervention with a Class IIa ESC recommendation. This is one area where supplementation (via fortified foods) has robust RCT evidence.</i>
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Curcumin, Berberine & Other High-Interest Phytochemicals

Strong Mechanisms, Variable Clinical Evidence

Curcumin — High Mechanism, Low Bioavailability

Curcumin is the primary active polyphenol in turmeric (*Curcuma longa*). It has been studied in over 120 completed clinical trials and has demonstrated potent anti-inflammatory, antioxidant, anti-cancer, and metabolic effects in laboratory and early clinical studies. Its major limitation is extremely poor oral bioavailability — rapidly metabolized and eliminated before reaching significant tissue concentrations.

Curcumin Mechanism	Clinical Application	Evidence Level
NF-κB inhibitor (binds IKK-beta directly — one of the most potent natural NF-κB inhibitors known)	Osteoarthritis: 1g/day curcumin comparable to NSAIDs (ibuprofen equivalent) for knee pain in RCTs	Moderate — consistent positive RCTs in OA; effect comparable to NSAIDs at standard doses
AMPK activator + PPARγ agonist (insulin sensitizing)	Pre-diabetes: T2DM conversion reduced by 78% vs placebo over 9 months (n=240 RCT). Reduces HOMA-IR in metabolic syndrome.	Moderate — notable pre-diabetes RCT; metabolic syndrome data consistent across multiple small RCTs
Nrf2 activator (inducible antioxidant enzyme expression)	NAFLD: improved liver enzyme levels (ALT), reduced liver steatosis in RCTs	Moderate — multiple RCTs in NAFLD; liver-specific benefits most consistent
HDAC inhibitor + direct anti-tumor effects in cell models	Cancer prevention: Phase 2 trials in colorectal cancer show colonocyte penetration; Phase 3 trials ongoing	Preliminary — compelling mechanistic data; Phase 3 trial results awaited

CAUTION

Standard turmeric in cooking delivers minimal pharmacological curcumin — estimated 2-5% absorption of a small amount. For therapeutic effects demonstrated in clinical trials, bioavailability-enhanced formulations are necessary: piperine (black pepper) increases curcumin half-life 20-fold (BioPerine); lipid-formulated (phospholipid complex, phytosome); or nanoparticle/liposomal preparations. Counsel patients: cooking with turmeric is beneficial for its modest anti-inflammatory effect, but clinical trial doses require standardized supplements.

Berberine — The Phytochemical Most Comparable to a Drug

Berberine is an alkaloid found in *Berberis* (barberry), *goldenseal*, and *Coptis* species. It is one of the most pharmacologically active phytochemicals known — activating AMPK through the same pathway as metformin (inhibiting mitochondrial Complex I → raising AMP:ATP ratio → AMPK activation) and inhibiting PCSK9 (the enzyme that degrades LDL receptors — the same target as the PCSK9 inhibitor drugs).

Berberine Effect	Mechanism	Clinical Evidence
Reduces fasting blood glucose and HbA1c	AMPK activation → improved GLUT4 expression and glucose uptake; reduces hepatic glucose output	Meta-analysis (14 RCTs): berberine comparable to metformin for FPG, HbA1c, and triglyceride reduction in T2DM patients. This is one of the strongest phytochemical-to-drug comparisons in the literature.
Reduces LDL cholesterol	Inhibits PCSK9 → increases LDL receptor recycling on hepatocytes → more LDL cleared from blood	Meta-analysis: berberine reduces LDL-C by ~25mg/dL — clinically meaningful, comparable to low-dose statins in mild hypercholesterolaemia
Gut microbiome modulation	Increases short-chain fatty acid-producing bacteria; reduces inflammatory dysbiosis	May explain part of its metabolic effect — a gut-mediated mechanism in addition to direct AMPK and PCSK9 effects
PCOS management	Improves insulin sensitivity and hormonal profile in PCOS	Several RCTs show berberine comparable to metformin in PCOS — with a potentially better lipid profile improvement

CAUTION

Berberine has genuine pharmacological potency — which means it also has genuine drug interaction potential. It inhibits CYP3A4 and P-glycoprotein, potentially increasing blood levels of many drugs including cyclosporine, some antibiotics, and anticoagulants. It should not be combined with metformin without medical supervision (additive hypoglycaemic effect). Unlike most phytochemicals where the concern is insufficient effect, berberine's concern is that it is effective enough to cause interactions. Treat it as a supplement with drug-like properties.

PART THREE — Bioavailability: Why the Same Food Affects People Differently

One of the most important and underappreciated aspects of phytochemical science is that the same food can deliver very different amounts of active phytochemicals to different people — depending on how the food was prepared, what was eaten with it, and critically, what bacteria live in the person's gut. This explains why clinical trials of phytochemicals show wide individual variation, and why blanket supplement recommendations for isolated compounds often fail.

The Four Bioavailability Determinants

Factor	How It Affects Phytochemical Delivery	Practical Implication
Food preparation and cooking method	Myrosinase (cruciferous vegetables) is heat-labile — boiling destroys it, preventing ITC formation. Lycopene (tomatoes) bioavailability is increased by cooking and fat co-ingestion. Quercetin is partially lost in boiling water. Allicin requires mechanical damage (chopping/crushing) plus 10 minutes before cooking.	The 'how you cook it' question is as important as 'what you eat' for phytochemical delivery. This is why food preparation education is an essential component of phytochemical-focused dietary counselling.
Food matrix and fat co-ingestion	Carotenoids (lycopene, beta-carotene, lutein), curcumin, and other fat-soluble phytochemicals are absorbed dramatically better when consumed with fat (2-10x improvement). Low-fat dressings on salads substantially reduce carotenoid absorption.	Add olive oil, avocado, nuts, or seeds to salads and vegetable dishes — not just for their own nutritional value, but to enhance phytochemical absorption from the vegetables. This is another reason why low-fat plant-based diets may not maximize phytochemical bioavailability.
Gut microbiome — the primary transformer	Many phytochemicals are inactive until gut bacteria convert them to bioactive forms. Ellagitannins → urolithins (requires Gordonibacter and Ellagibacter species). Isoflavones → equol (requires Slackia isoflavoniconvertens — present in only ~30% of Western adults but ~60% of Asian adults). Lignans → enterolactone (requires Lactonifactor longoviformis).	Individual response to soy foods, pomegranate, and flaxseed depends on which bacteria the individual harbours. This explains population-level differences in phytochemical health effects and why the same RCT food intervention shows wide individual variation.
Phase II metabolism in the intestine and liver	Polyphenols are rapidly glucuronidated, sulfated, and methylated in intestinal cells and the liver — reducing their half-life in blood. Aglycone forms (without sugar) are generally more bioavailable than glycoside forms (with sugar). Piperine from black pepper inhibits glucuronidation, increasing many polyphenols' half-life.	The brief window of plasma polyphenol activity means consistent daily intake is more effective than occasional large doses. Fermented foods (where gut bacteria have already deglycosylated polyphenols before consumption) may provide more bioavailable forms.

The Gut Microbiome as Phytochemical Transformer

The relationship between dietary phytochemicals and the gut microbiome is bidirectional and clinically important. Phytochemicals modulate the microbiome (acting as prebiotics, selectively feeding beneficial bacteria). And the microbiome transforms phytochemicals into more potent bioactive compounds. Disrupting the microbiome through antibiotics, ultra-processed food, or low dietary fibre simultaneously reduces the phytochemical benefit of an otherwise good diet.

Phytochemical	What Gut Bacteria Do to It	Why This Matters
Ellagitannins (pomegranate, walnuts, raspberries, strawberries)	Gordonibacter and Ellagibacter species convert ellagitannins → urolithins A, B, C. Urolithin A activates mitophagy (cellular cleanup of damaged mitochondria) and mitochondrial biogenesis — effects not present in the parent ellagitannin.	~40% of people are 'urolithin producers' with the right bacteria; ~60% are non-producers or produce only less active forms. A person's response to pomegranate consumption depends entirely on their microbiome, not just their dietary intake. Clinical trials of Mitopure (purified urolithin A) bypass this by supplementing the bioactive compound directly.
Isoflavones — daidzein (from soy)	Slackia isoflavoniconvertens and Lactococcus sp. convert daidzein → equol. Equol is a more potent phytoestrogen than daidzein itself and is responsible for most of the hormonal and cancer-protective effects attributed to soy.	~30% of Western adults produce equol; ~50-60% of Asian adults (explaining why soy-cancer protection evidence is stronger in Asian than Western populations). Equol production can be enhanced by increasing dietary fibre and fermented food intake — cultivating the relevant bacteria.
Lignans from flaxseed and whole grains	Lactonifactor longoviformis and Blautia producta convert SDG (secoisolariciresinol diglucoside) → enterodiol → enterolactone	Enterolactone plasma levels inversely associated with breast cancer risk and cardiovascular mortality in prospective studies — but enterolactone production requires specific bacteria that may be absent or reduced in antibiotic users, people on low-fibre diets, or those with IBD.
Chlorogenic acids from coffee	Colonic bacteria convert chlorogenic acids into dihydrocaffeic acid and dihydroferulic acid — compounds that may be partly responsible for coffee's protective effects	Even when coffee polyphenols are poorly absorbed in the small intestine, their transformation products in the colon enter the circulation and reach tissues — extending the window of bioactivity well beyond the initial absorption phase.

PRACTICE

The microbiome implication for dietary counselling: recommending phytochemical-rich foods is necessary but not sufficient if the patient's microbiome cannot transform them. Simultaneously: increase dietary fibre (feeds bacteria that transform phytochemicals); include fermented foods (adds relevant transforming bacteria); reduce antibiotic overuse; reduce ultra-processed food intake (which reduces microbiome diversity). Phytochemical recommendations and microbiome health recommendations are inseparable.

PART FOUR — The Evidence: What We Know, What We Think We Know, and What We Don't

A critical skill for clinical dietitians is the ability to accurately assess the strength of evidence for a phytochemical health claim — to distinguish between what has been demonstrated in randomized controlled trials versus what is supported only by epidemiological associations or laboratory data. The following framework classifies the major phytochemicals by evidence level.

Evidence Level	What It Means	Phytochemicals at This Level
STRONG — RCT evidence for clinical outcomes	Randomized controlled trials showing a meaningful effect on a clinically relevant endpoint (not just a biomarker)	Plant sterols: 2g/day → 10% LDL reduction (>100 RCTs). Lutein+zeaxanthin: 25% reduction in AMD progression (AREDS2). Cocoa flavanols: 21% reduction in CVD mortality (COSMOS). Garlic extract: reduces cholesterol and BP (39-RCT meta-analysis). Berberine: comparable to metformin for glucose and lipids (multiple RCTs).
MODERATE — Consistent epidemiological + biomarker RCTs	Strong consistent inverse associations in large cohort studies + mechanistic plausibility + RCT evidence on intermediate biomarkers (not final clinical outcomes)	Quercetin: BP reduction in meta-analysis of RCTs; CVD mortality associations in large cohorts. Sulforaphane: reduced carcinogen DNA adducts in human trial; preclinical cancer evidence strong. Lycopene: ~40% prostate cancer risk reduction in cohort data; Phase 2 trial data. Curcumin: OA pain, NAFLD, pre-diabetes RCTs positive. Chlorogenic acid (coffee): T2DM risk reduction in >28 cohort studies; decaffeinated coffee equally protective.
PRELIMINARY — Mechanistic + early phase trials	Compelling mechanisms in cell and animal models; Phase 1/2 clinical data; promising but not yet practice-changing	Resveratrol: strong mechanistic data (SIRT1, AMPK), limited clinical translation due to bioavailability. Urolithins: Phase 2 trial data on muscle function in elderly. Fisetin (strawberries): senolytic activity in early human trials. Berberine in PCOS: multiple positive RCTs but smaller studies. Astaxanthin: exercise performance RCTs positive; NAFLD early trial data.
INSUFFICIENT — Associations only or conflicting data	Interesting but not yet ready for clinical recommendation	Many specific phytochemicals in isolation. Resveratrol cardiovascular outcomes (neutral in RCTs despite mechanistic promise). Most specific carotenoid-cancer associations beyond lycopene-prostate. Isolated supplement interventions for cancer prevention in generally healthy populations.

CAUTION

A critical clinical warning: the categories above apply to whole food sources of phytochemicals unless specifically noted as supplement evidence. In several cases (beta-carotene, vitamin E, selenium at excess doses), supplement trials showed harm while dietary intake remains protective. Never extrapolate positive evidence from food-based phytochemical research to isolated high-dose supplement recommendations without checking specifically for supplement trial data.

Clinical Scenario: Applying Phytochemical Knowledge in Practice

- Fatima is a 48-year-old nurse with a family history of breast cancer, pre-diabetes (FPG 108 mg/dL, HbA1c 6.1%), and mild hypercholesterolaemia (LDL 152 mg/dL). She is postmenopausal (natural menopause at 46), non-smoker, does not drink coffee ('I was told it's bad for health'), and eats a diet that is moderate in vegetables but heavy in refined grains and processed foods. She has heard that 'antioxidant supplements' and 'soy isoflavones' are good for breast cancer prevention and asks your advice.
- Question 1: Which phytochemical-rich foods would have the strongest evidence base for reducing Fatima's three clinical concerns (breast cancer family history, pre-diabetes, hypercholesterolaemia)? Identify at least 6 specific foods and explain the mechanism for each.
- Question 2: She asks specifically about soy isoflavone supplements for breast cancer prevention. What does the evidence show — and is this safe for her? How does her postmenopausal status affect your recommendation?
- Question 3: She avoids coffee based on advice she received years ago. What would you tell her about the evidence on coffee and her specific health concerns?
- Question 4: She is enthusiastic about phytochemicals and wants to take a comprehensive 'antioxidant supplement' containing beta-carotene, vitamin E, and lycopene. What is your evidence-based response?
- Question 5: Fatima mentions she has been on antibiotics for a urinary tract infection for the past 3 weeks. How does this affect the phytochemical benefit she is receiving from her diet — and what would you recommend?

Critical Thinking Questions

- Berberine is described in this lecture as having clinical evidence comparable to metformin for glucose control in T2DM. If a patient with pre-diabetes asks whether they can use berberine instead of metformin, what is your role as a dietitian in this conversation? What factors would determine your response — and what would you advise?
- The gut microbiome section explains that approximately 40% of people cannot convert ellagitannins to urolithins, and only ~30% of Western adults produce equol from soy isoflavones. This means the same dietary recommendation will have very different effects in different patients. How does this individuality of phytochemical response challenge the way we currently provide dietary advice — and what practical tools are available to account for it?
- The lecture notes that garlic and onion are already central to Sudanese cuisine, and that coffee consumption is culturally widespread. How does understanding the phytochemical science of these foods change your approach to dietary counselling in Sudanese populations — and what other traditional foods from Sudan and East Africa might deserve attention from a phytochemical perspective?

Lecture Summary — Key Takeaways for Dietetic Practice

- Phytochemicals are biologically active plant compounds that are not essential nutrients but that contribute substantially to the health-protective effects of plant-rich diets. They work through four primary mechanisms: Nrf2 activation (switches on antioxidant and detoxification genes); NF-κB suppression (reduces chronic inflammation); AMPK activation (improves metabolic function); and gut microbiome transformation (converts inactive forms to potent bioactive).
- Major families and their strongest evidence: Flavonoids (quercetin → BP; cocoa flavanols → CVD mortality; anthocyanins → endothelial function and T2DM); Phenolic acids (chlorogenic acid from coffee → 25-30% T2DM reduction); Glucosinolates/sulforaphane (broccoli → Nrf2/cancer prevention, carcinogen blocking, glucose reduction in T2DM RCTs); Allium organosulfur compounds (garlic → LDL, cholesterol, BP reduction across 39 RCTs); Carotenoids (lutein/zeaxanthin → AMD prevention RCT evidence; lycopene → prostate cancer in cohort data); Phytosterols (2g/day → 10% LDL reduction — strongest phytochemical-LDL RCT evidence); Berberine (comparable to metformin in T2DM RCTs — treat as a pharmacologically active compound with drug interactions).
- Bioavailability is shaped by preparation (myrosinase destroyed by boiling — steam cruciferous vegetables; lycopene increased by cooking with fat; allicin requires crushing then 10 minutes rest before heat); fat co-ingestion (2-10x improvement for fat-soluble phytochemicals); gut microbiome (urolithins from ellagitannins, equol from isoflavones, enterolactone from lignans — all require specific gut bacteria); and phase II metabolism (rapid conjugation limits half-life; consistent daily intake is more effective than occasional large doses).
- Evidence hierarchy: STRONG (plant sterols, lutein/zeaxanthin for AMD, cocoa flavanols, garlic, berberine). MODERATE (quercetin, sulforaphane, lycopene, curcumin, coffee). PRELIMINARY (resveratrol, urolithins, fisetin, astaxanthin). Never extrapolate whole-food evidence to high-dose isolated supplements without specifically checking supplement trial data — beta-carotene and vitamin E at supplement doses have caused harm.
- Grapefruit drug interaction: furanocoumarins irreversibly inhibit CYP3A4 for 24-72 hours — significantly increases blood levels of statins, cyclosporine, amlodipine, midazolam, and many other drugs. This is a clinical safety issue requiring patient education.
- Practical counselling principles: recommend dietary patterns over supplements; connect traditional/cultural food practices to phytochemical science (garlic, onion, turmeric, coffee in Sudanese/African contexts); teach preparation matters (steam vs boil, add fat to salads, crush garlic before cooking); support microbiome health (fibre, fermented foods) as a prerequisite for phytochemical benefit; assess evidence level before recommending any supplemental phytochemical.

Suggested reading:

1. Manach C et al. (2004). Polyphenols: food sources and bioavailability. American Journal of Clinical Nutrition. |
2. Rowland I et al. (2018). Gut microbiota composition in relation to the metabolic transformation of phytochemicals. European Journal of Nutrition. |
3. Dinkova-Kostova AT & Talalay P (2008). Direct and indirect antioxidant properties of inducers of cytoprotective proteins. Molecular Nutrition & Food Research. |
4. COSMOS Investigators (2022). Cocoa supplement and multivitamin outcomes study. American Journal of Clinical Nutrition. |
5. Vuorisalo T & Arjamaa O (Eds.). Evolution of Obesity. Chapter on plant secondary metabolites and human health.

Module 2 — Body Regulation & Composition

Internal Balance & Physical Assessment

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Fluids & Electrolytes

Body Fluid Compartments, Electrolyte Physiology, pH Balance & Clinical Disorders

- ▶ Part 1: Body Water — Compartments, Forces & Osmolality
- ▶ Part 2: The Water Regulation System — ADH, Thirst & SIADH
- ▶ Part 3: Sodium — Hyponatraemia, Hypernatraemia & Correction Rates
- ▶ Part 4: Potassium — Membrane Potential, Hypokalaemia & Hyperkalaemia
- ▶ Part 5: Chloride, Bicarbonate & the Four Acid-Base Disturbances
- ▶ Part 6: Clinical Application — Refeeding Syndrome | GI Losses | Parenteral Nutrition
- ▶ Clinical Case: Amira — Anorexia Nervosa, Collapse & Electrolyte Emergency

Fluids & Electrolytes

Water Balance, Osmolarity, Sodium, Potassium, Chloride & Acid-Base Regulation — From Mechanism to Patient

Focus: Understanding why the body needs precise fluid and electrolyte balance — and what happens to patients when it fails

Why Fluid and Electrolyte Balance Matters: The Clinical Framework

The human body is approximately 60% water by weight, and every cell, organ, and physiological process depends on maintaining the volume, composition, and distribution of that water within extraordinarily tight tolerances. Serum sodium varies by less than 2% in health. Total body water is regulated within 0.1% precision on a daily basis despite enormous variation in intake and losses. When these systems fail — from disease, medication, inadequate intake, or excessive losses — the consequences are rapid and potentially fatal.

WHY?

This lecture is not about memorizing electrolyte reference ranges. It is about understanding the systems that maintain those ranges — so that when a patient presents with abnormal values, you can reason through why it happened, what clinical syndrome is present, and what the appropriate nutritional and clinical response is. Fluid and electrolyte disturbances are among the most common clinical problems encountered across all patient populations, including post-surgical patients, critically ill patients, patients with kidney disease, heart failure, liver disease, and any patient receiving enteral or parenteral nutrition.

Learning Outcomes — By the end of this lecture, students will be able to:

- Describe the distribution of body fluids across compartments and explain the forces that govern fluid movement between them
- Explain how the body regulates water balance through osmolarity sensing, ADH, and thirst and what happens when these systems fail
- Describe the physiological roles of sodium, potassium, and chloride, and the clinical consequences of deficiency and excess for each
- Classify and mechanistically explain the common fluid disturbances: dehydration, overhydration, hyponatraemia, and hypernatraemia
- Explain the body's acid-base buffer systems and describe the four primary acid-base disturbances with their clinical contexts
- Apply fluid and electrolyte knowledge to clinical nutrition practice: enteral feeding, parenteral nutrition, diarrhoea, vomiting, refeeding syndrome, and hot climate adaptation

PART ONE — Body Water: Where It Is and How It Moves

Understanding fluid and electrolyte physiology begins with understanding where body water resides and what controls its movement between compartments.

Body Fluid Compartments

Distribution, Composition and the Forces That Separate Them

The Two Major Compartments

Compartment	Approximate Volume (70 kg adult)	% of Body Weight	Key Electrolyte Composition
Total Body Water (TBW)	42 litres	60%	Water + all dissolved solutes
Intracellular Fluid (ICF)	28 litres	40%	Dominant cation: K^+ (140 mEq/L); Mg^{2+} ; phosphate (HPO_4^{2-}); proteins
Extracellular Fluid (ECF)	14 litres	20%	Dominant cation: Na^+ (140 mEq/L); dominant anion: Cl^- + HCO_3^-
→ Intravascular (plasma)	3 litres	4-5%	Na^+ 140; Cl^- 103; HCO_3^- 24; protein (albumin, globulins) as oncotic force
→ Interstitial fluid	11 litres	15-16%	Similar to plasma but protein-free (capillary barrier excludes most protein)
Transcellular fluid	1-2 litres	1-2%	CSF, synovial fluid, GI secretions, pleural fluid, peritoneal fluid

WHY?

The key to understanding fluid movement is that water is passive — it follows solutes. When solute concentration is higher in one compartment, water moves in to equalize. This is the fundamental principle behind every fluid disturbance: something has altered the solute distribution between compartments, and water has moved in response. Understanding which compartment has gained or lost solute is the first step in diagnosing any fluid disturbance.

The Forces Governing Fluid Movement

Force	What It Is	Where It Acts	Clinical Relevance
Osmotic pressure	Created by dissolved solutes (mainly Na ⁺ in ECF, K ⁺ in ICF) that cannot freely cross membranes	Across cell membranes (ICF vs ECF)	Changes in serum Na ⁺ alter osmolarity → cause water to move into or out of cells → cell swelling or shrinking. Rapid correction of hyponatraemia can cause osmotic demyelination because brain cells adapt to chronic hypo-osmolarity.
Oncotic (colloid osmotic) pressure	Created specifically by large plasma proteins (principally albumin) that cannot cross capillary walls	Across capillary walls (plasma vs interstitium)	Albumin holds water within the vascular space. Hypoalbuminaemia (malnutrition, liver disease, nephrotic syndrome) → reduced oncotic pressure → oedema. IV albumin administration temporarily restores oncotic pressure.
Hydrostatic pressure	Blood pressure within capillaries that pushes fluid out of vessels into interstitium	Across capillary walls	Elevated venous pressure (heart failure, venous obstruction) → increased capillary hydrostatic pressure → oedema. Blood pressure medications affect this balance.
Starling forces	The net balance of oncotic and hydrostatic pressures at the capillary (Starling equation)	Across capillary walls	Net fluid movement = filtration pressure (outward) minus reabsorption pressure (inward). When Starling forces are disrupted — by low albumin, high venous pressure, or increased capillary permeability (sepsis) — oedema results.

CONNECT

Albumin as a fluid management tool: A serum albumin below 25 g/L significantly impairs oncotic pressure maintenance in the vascular space. This is relevant not just for oedema management but for nutritional support: patients receiving adequate protein and energy who remain oedematous due to low albumin need both nutritional correction of the underlying protein deficit AND understanding that oedema resolution will be slow while albumin synthesis recovers. Liver disease (impaired synthesis) and nephrotic syndrome (urinary albumin loss) are the two main causes beyond malnutrition.

Osmolarity vs. Osmolality — The Key Measurement

Osmolarity refers to the number of osmotically active particles per litre of solution (mOsm/L). Osmolality refers to particles per kilogram of solvent (mOsm/kg) — the clinically measured value. The two are nearly equivalent in dilute biological solutions. Normal serum osmolality is 275-295 mOsm/kg.

Calculated serum osmolality = $2 \times [\text{Na}^+] + [\text{Glucose}/18] + [\text{BUN}/2.8]$

In most clinical situations, the simplified formula $2 \times [\text{Na}^+]$ approximates well, because sodium (and its accompanying anions) accounts for ~95% of extracellular osmolality. This means serum sodium IS essentially a proxy for serum osmolality — and serum osmolality IS the primary driver of ADH secretion and thirst.

Condition	Serum Na ⁺	Serum Osmolality	What Has Happened
Normal	135-145 mEq/L	275-295 mOsm/kg	Water and sodium in normal proportion
Hyponatraemia (hypotonic)	<135 mEq/L	<275 mOsm/kg	Excess water relative to sodium → cells swell with water influx
Hypernatraemia	>145 mEq/L	>295 mOsm/kg	Sodium excess relative to water → cells shrink with water efflux
Isotonic hyponatraemia (pseudohyponatraemia)	<135 mEq/L	Normal 275-295	Severe hyperlipidaemia or hyperproteinaemia artifactually lowers measured Na ⁺ ; osmolality is actually normal; cells are not affected
Hypertonic hyponatraemia	<135 mEq/L	>295 mOsm/kg	High glucose or other osmoles (mannitol) draw water from ICF to ECF → dilutes Na ⁺ ; but cells are actually shrinking, not swelling

PART TWO — The Water Regulation System

The body regulates total body water through a tightly coordinated system involving osmosensors in the hypothalamus, the hormone ADH (antidiuretic hormone, also called vasopressin), and the kidneys. Thirst is the backup system when ADH cannot compensate alone. Understanding this system is essential for understanding hyponatraemia, hypernatraemia, and SIADH.

The ADH-Thirst-Kidney Axis

How the Body Detects and Corrects Water Imbalance

Stimulus	Response	Where It Acts	Physiological Effect
↑ Serum osmolality (>295 mOsm/kg) — dehydration signal	↑ ADH release from posterior pituitary + ↑ thirst	ADH acts on renal collecting duct principal cells via V2 receptors → inserts aquaporin-2 water channels → water reabsorption	Urine becomes concentrated (osmolality up to 1200 mOsm/kg); dilute urine volume falls; plasma osmolality returns toward normal
↓ Serum osmolality (<275 mOsm/kg) — overhydration signal	↓ ADH release; thirst suppressed	Without ADH, collecting duct is water-impermeable → large volume of dilute urine produced	Excess water excreted; plasma osmolality rises toward normal
↓ Blood volume/pressure — volume depletion signal (stronger override)	↑ ADH even if osmolality is normal or low; also activates RAAS	ADH (water retention); Angiotensin II (vasoconstriction + aldosterone → Na ⁺ retention)	Maintains blood pressure at the cost of osmolality — explains hyponatraemia in volume-depleted states (the body sacrifices osmolality to preserve volume)
Normal plasma osmolality + normal volume	Basal low ADH; urine volume ~1-2 L/day	Allows some water excretion to match intake	Steady state: water intake = water output

WHY?

The volume-over-osmolality override is the most clinically important principle in fluid physiology. When the body is volume-depleted (haemorrhage, severe dehydration, heart failure with low output), it will secrete ADH and retain water even if serum sodium is already low. This is why patients with severe vomiting or diarrhoea, heart failure, or cirrhosis develop hyponatraemia — the volume-sensing system overrides the osmolality system and the body retains water despite dilution of sodium. Treating the sodium alone without addressing the underlying volume problem will not work.

SIADH — The Most Clinically Common ADH Disorder

Syndrome of Inappropriate ADH Secretion (SIADH) occurs when ADH is secreted continuously without appropriate osmotic or volume stimuli. The result is water retention, dilutional hyponatraemia, and inappropriately concentrated urine despite low serum osmolality.

Cause of SIADH	Mechanism	Common Clinical Context
CNS disorders	Brain injury, meningitis, encephalitis, stroke, subdural haematoma → hypothalamic ADH dysregulation	Common in neurosurgical and neuro-ICU patients; consider in any patient with unexplained hyponatraemia following CNS event
Pulmonary disorders	Pneumonia, TB, empyema, mechanical ventilation with PEEP	Positive pressure ventilation reduces venous return → atrial natriuretic peptide decreases → ADH uninhibited
Medications	SSRIs, SNRIs, carbamazepine, cyclophosphamide, vincristine, NSAIDs, PPIs, opioids	SSRIs and SNRIs are the most commonly encountered cause in outpatient settings; check medication list in any hyponatraemia
Malignancy (ectopic ADH)	Small cell lung cancer, pancreatic cancer, lymphoma produce ADH directly	Paraneoplastic syndrome — hyponatraemia may be the presenting feature of an occult malignancy
Surgery and pain	Postoperative ADH release (pain, anaesthesia, nausea, hypovolaemia stimulate ADH)	Hypotonic IV fluids (0.45% NaCl, 5% dextrose) in postoperative patients with high ADH → dangerous dilutional hyponatraemia

CAUTION

SIADH diagnostic criteria: (1) Hyponatraemia with low serum osmolality (<275 mOsm/kg); (2) Inappropriately concentrated urine (Uosm >100 mOsm/kg, typically >300); (3) Urine Na⁺ >30 mEq/L (kidneys are excreting Na⁺ because volume is normal/expanded); (4) Clinical euvolaemia (no oedema, no dehydration); (5) Normal adrenal, thyroid, and renal function. Treatment: fluid restriction (800-1000 mL/day) is first-line for mild-moderate SIADH. Salt tablets, loop diuretics, and vasopressin receptor antagonists (tolvaptan) are used for severe or refractory cases.

PART THREE — Sodium: The Extracellular Osmole

Sodium is the dominant extracellular cation and the primary determinant of extracellular fluid volume and osmolality. Serum sodium concentration reflects the ratio of sodium to water in the ECF — not simply the absolute amount of sodium in the body. This is the most commonly misunderstood aspect of sodium physiology.

Sodium Physiology

The Central Cation of the Extracellular Fluid

What Sodium Does

Function	Mechanism	Clinical Consequence of Disturbance
Controls extracellular fluid volume	Na^+ is the primary osmole of the ECF; water follows Na^+ ; ECF volume = $f(\text{total body Na}^+)$	Oedema = excess total body Na^+ ; dehydration = deficit of total body Na^+ . Note: serum concentration can be normal while total body amount is abnormal.
Determines ECF osmolality	Serum $[\text{Na}^+] \times 2 \approx$ serum osmolality in most clinical situations	Changes in serum Na^+ directly change the osmotic gradient across cell membranes, causing water to move between ICF and ECF
Enables action potentials	Na^+ influx through voltage-gated Na^+ channels depolarizes nerve and muscle cell membranes	Severe hyponatraemia $\rightarrow$ neuronal swelling $\rightarrow$ confusion, seizures, coma. Severe hypernatraemia $\rightarrow$ neuronal shrinkage $\rightarrow$ tremor, seizures, death.
Drives secondary active transport	Na^+ - K^+ -ATPase creates the Na^+ gradient used to drive glucose, amino acid, and other nutrient absorption (SGLT1, etc.)	Hyponatraemia impairs these co-transport mechanisms; relevant in severe malabsorptive states
Regulated by aldosterone	Aldosterone (from adrenal cortex) stimulates Na^+ reabsorption in collecting duct principal cells via ENaC	Hyperaldosteronism $\rightarrow$ Na^+ retention + K^+ wasting; Addison's disease (adrenal insufficiency) $\rightarrow$ Na^+ loss + K^+ retention

Hyponatraemia — The Most Common Electrolyte Disturbance

Hyponatraemia (serum $\text{Na}^+ < 135$ mEq/L) is the most common electrolyte abnormality in hospitalized patients, occurring in approximately 15-30% of all hospital admissions. It is not a single disease but a syndrome with multiple causes, grouped by volume status.

Volume Status	Serum Na ⁺	Total Na ⁺ Body	Total Body Water	Common Causes	Key Clinical Features
HYPOVOLAEMIC (volume-depleted)	Low	Low (but water lost proportionally more)	Low	GI losses (vomiting, diarrhoea, high-output fistula); renal losses (diuretics, Addison's, salt-wasting nephropathy); third-spacing (burns, pancreatitis)	Signs of dehydration: dry mucous membranes, tachycardia, low JVP, orthostatic hypotension, oliguria. Urine Na ⁺ <20 mEq/L if extrarenal losses; >20 if renal losses
EUVOLAEMIC (normal volume)	Low	Normal	High	SIADH (most common); hypothyroidism; glucocorticoid deficiency; polydipsia (psychiatric or iatrogenic); marathon runners; beer potomania	No oedema, no dehydration. Urine Na ⁺ >30, urine Osm >100. Treat with fluid restriction and address underlying cause.
HYPERVOLAEMIC (volume-expanded)	Low	High (but water increased proportionally more)	High	Congestive heart failure (low effective arterial volume stimulates ADH); hepatic cirrhosis; nephrotic syndrome; CKD	Oedema, ascites, pleural effusions. Paradoxically, these patients are volume-overloaded but have low effective arterial blood flow, so ADH remains high. Urine Na ⁺ <20 mEq/L in cardiac and hepatic causes.

Clinical Manifestations of Hyponatraemia

The symptoms of hyponatraemia are caused by cerebral oedema — water moves from the hypotonic ECF into brain cells, causing them to swell. The severity of symptoms depends more on the rate of fall than the absolute level.

Serum Na ⁺	Rate of Development	Typical Symptoms
>125 mEq/L	Any rate	Usually asymptomatic; mild nausea, malaise possible
120-125 mEq/L	Acute (<48h)	Headache, nausea, vomiting, lethargy, confusion
120-125 mEq/L	Chronic (>48h)	Often asymptomatic or mild — brain has adapted by exporting organic osmolytes
<120 mEq/L	Any rate	Severe neurological symptoms: seizures, coma, respiratory arrest, death. Most dangerous is acute severe hyponatraemia.

CAUTION

Osmotic Demyelination Syndrome (ODS) — previously called central pontine myelinolysis: When chronic hyponatraemia is corrected too rapidly, the brain (which has adapted to low osmolality by exporting osmolytes) is suddenly exposed to rising osmolality and shrinks. This causes demyelination of neurons in the pons and other areas. Result: locked-in syndrome, dysarthria, dysphagia, quadriplegia. Safe correction rate: no more than 8-10 mEq/L per 24 hours for chronic hyponatraemia (or 10-12 mEq/L per 24h for acute). If accidentally over-corrected, can give free water (D5W or desmopressin) to lower Na⁺ back.

Hypernatraemia — Always Means Water Deficit Relative to Sodium

Hypernatraemia (serum Na⁺ >145 mEq/L) essentially always reflects a deficit of free water relative to sodium. It can occur through water loss without sodium replacement (most common), or rarely through sodium gain. The thirst mechanism is the primary defence — hypernatraemia in a conscious patient with access to water and intact thirst implies the thirst mechanism is impaired or overridden.

Cause	Example	Clinical Context
Inadequate water intake	Inability to drink (coma, sedation, dysphagia, infancy, elderly dementia); no access to water	The most common cause in hospital. Patients dependent on others for water access — ICU, nursing home, post-stroke — are most vulnerable.
Insensible water losses (hypotonic)	Fever (each 1°C rise → ~150 mL/day extra loss), tachypnoea, sweating, burns, open wounds	In hot climates like Sudan, fever + inadequate oral fluid replacement is a common cause. Children and the elderly are most vulnerable.
Renal water loss — Diabetes Insipidus (DI)	Central DI: no ADH production (head trauma, pituitary surgery, infiltrative disease). Nephrogenic DI: kidney cannot respond to ADH (lithium toxicity, hypercalcaemia, hypokalaemia, hereditary)	Massive dilute urine (polyuria >3 L/day) + hypernatraemia if patient cannot match water losses. Urine Osm <300 mOsm/kg despite high serum Osm.
GI losses	Diarrhoea (particularly in infants — hypotonic relative to plasma if Na ⁺ concentration in stool is low), osmotic diarrhoea	Watery diarrhoea can cause hypernatraemic dehydration in infants and children because stool water loss is proportionally greater than sodium loss
Sodium gain (rare)	Hypertonic saline infusion, sodium bicarbonate overdose, inadvertent high-salt feeding in tube-fed patients	Can occur in tube-fed patients receiving formula with high renal solute load without adequate free water flushes

CONTEXT

In Sudan and hot-climate regions of Sub-Saharan Africa and the Middle East, hypernatraemic dehydration in infants and children is a significant public health concern. Acute diarrhoeal illness combined with high ambient temperatures and inadequate oral rehydration leads to combined water and electrolyte losses that can rapidly become dangerous. ORS (Oral Rehydration Solution) with the correct sodium concentration (90 mEq/L for acute diarrhoea; 75 mEq/L per WHO 2002 formula) is the primary preventive and therapeutic intervention. Community health workers and caregivers need to know how to prepare and administer ORS correctly.

PART FOUR — Potassium: The Intracellular Cation

Potassium is the dominant intracellular cation, with 98% of total body potassium inside cells (predominantly muscle cells). The ratio of intracellular to extracellular potassium concentration determines the resting membrane potential of excitable cells (nerves and muscles), making potassium disorders among the most immediately dangerous electrolyte abnormalities.

Potassium Physiology

The Membrane Potential Electrolyte

Function	Mechanism	Clinical Consequence of Disturbance
Sets resting membrane potential	The K ⁺ concentration gradient across the cell membrane (ICF 140 mEq/L : ECF 4 mEq/L = 35:1 ratio) determines the resting membrane potential of approximately -90 mV, set by the Nernst equation	Any change in this ratio alters membrane excitability. Hypokalaemia → cell more negative (hyperpolarised) → requires stronger stimulus for action potential → muscle weakness, paralysis. Hyperkalaemia → cell less negative (depolarized) → spontaneous firing, arrhythmias.
Cardiac rhythm	Cardiac action potentials depend on K ⁺ -mediated repolarization (phase 3); K ⁺ channels open to return cell to resting potential	Hypokalaemia prolongs repolarization → U waves, QT prolongation, ventricular fibrillation risk. Hyperkalaemia → peaked T waves, wide QRS, sine wave pattern → cardiac arrest (most dangerous emergency).
Muscle contraction	All excitable muscle cells depend on K ⁺ -mediated membrane potential for action potential generation and termination	Severe hypokalaemia (<2.5 mEq/L) → profound muscle weakness, paralysis including respiratory muscles. Hyperkalaemia → muscle weakness and paralysis through a different mechanism (persistent depolarization blocks firing).
Aldosterone regulation of K ⁺	High serum K ⁺ directly stimulates aldosterone secretion → increases K ⁺ excretion in collecting duct via ROMK	This is the primary defence against hyperkalaemia. Impaired in CKD, adrenal insufficiency, and with drugs that block

	channels; insulin and catecholamines drive K ⁺ into cells acutely	aldosterone (ACE inhibitors, ARBs, spironolactone, NSAIDs).
Acid-base interaction	H ⁺ and K ⁺ compete for renal excretion and cellular exchange: acidosis → H ⁺ moves into cells and K ⁺ moves out → hyperkalaemia; alkalosis → opposite → hypokalaemia	Every 0.1 unit fall in pH → approximately 0.6 mEq/L rise in serum K ⁺ . Treating acidosis will lower K ⁺ . Diabetic ketoacidosis: total body K ⁺ is depleted but serum K ⁺ appears normal/high; insulin therapy will drive K ⁺ into cells → hypokalaemia if not supplemented.

Hypokalaemia — Low Serum Potassium (<3.5 mEq/L)

Cause Category	Examples	Key Clinical Features
Inadequate intake	Prolonged fasting, anorexia nervosa, alcoholism, tea-and-toast diet, iatrogenic (low-K parenteral nutrition)	Gradual onset; becomes symptomatic when <3.0 mEq/L. Relevant in malnutrition assessment: chronic low dietary K ⁺ is common in highly processed diets.
Renal losses	Diuretics (thiazides, loop diuretics — most common drug cause); hyperaldosteronism; Bartter syndrome; Gitelman syndrome; renal tubular acidosis; hypomagnesaemia (impairs K ⁺ reabsorption)	Urine K ⁺ >30 mEq/L confirms renal wasting. Magnesium depletion causes refractory hypokalaemia — always check Mg ²⁺ and replace if low before expecting K ⁺ to correct.
Transcellular shift into cells	Insulin (endogenous surge post-meal or exogenous therapy), catecholamines (stress, beta-agonist therapy), alkalosis, refeeding syndrome	K ⁺ moves into cells without actual total body depletion; serum K ⁺ falls. Critical in refeeding syndrome: insulin surge drives K ⁺ (and phosphate, magnesium) into cells.
GI losses	Vomiting (direct K ⁺ loss is modest; secondary metabolic alkalosis + aldosterone activation causes renal K ⁺ wasting); diarrhoea (direct K ⁺ loss in stool — up to 30-50 mEq/L); laxative abuse; high-output ileostomy	Diarrhoea is a more significant direct K ⁺ source than vomiting. Ileostomy output can contain 10-15 mEq/L K ⁺ ; high output (>1500 mL/day) causes significant potassium loss.

CAUTION

Hypokalaemia + hypomagnesaemia: Magnesium is required for K⁺ retention in the renal tubule. Without adequate Mg²⁺, the ROMK channel remains open and K⁺ continues to leak into the tubular lumen. This means that hypokalaemia often cannot be corrected by potassium supplementation alone if magnesium is also depleted. In clinical practice: always check and correct magnesium when treating refractory hypokalaemia. This connection is particularly important in patients on loop diuretics (which cause both K⁺ and Mg²⁺ wasting) and in patients with alcoholism or malnutrition.

Hyperkalaemia — High Serum Potassium (>5.0 mEq/L)

Hyperkalaemia is the electrolyte disturbance most immediately life-threatening. At serum K^+ >6.5 mEq/L, cardiac arrest can occur without warning. This makes rapid recognition and intervention critical.

Cause	Mechanism	Management Principle
Pseudohyperkalaemia	Haemolysis of blood sample during venipuncture releases intracellular K^+ ; prolonged tourniquet use; very high WBC or platelet count release K^+ in clotted sample	Always repeat sample before treating if patient is asymptomatic and has no obvious cause. True hyperkalaemia: plasma K^+ normal; haemolysis: serum K^+ elevated.
Reduced renal excretion	CKD (most common chronic cause — GFR <30 mL/min impairs K^+ excretion); adrenal insufficiency (Addison's disease, hypoadosteronism); medications (ACE inhibitors, ARBs, spironolactone, NSAIDs, trimethoprim)	In CKD: dietary K^+ restriction; avoid K^+ -containing salt substitutes; monitor medications. Adrenal insufficiency: urgent corticosteroid replacement.
Transcellular shift out of cells	Insulin deficiency (DKA); acidosis (each 0.1 pH decrease $\rightarrow$ +0.6 mEq/L K^+); massive cell death (rhabdomyolysis, tumor lysis, haemolysis, burns)	Identify and treat the underlying cause. In DKA: insulin drives K^+ back into cells but requires K^+ supplementation as cells fill up. Tumor lysis syndrome: aggressive hydration, rasburicase.
Excessive intake	Potassium-containing IV fluids at high rates; salt substitutes (KCl) in CKD patients; high K^+ tube feed formula in CKD	Review all K^+ sources in the patient's medication and nutrition regimen. K^+ -containing IV fluids should be infused at <10 mEq/hour peripheral, <20 mEq/hour central.

PRACTICE

Acute hyperkalaemia management — the sequence matters: (1) Stabilize the cardiac membrane: IV calcium gluconate (does not lower K^+ but protects the heart within minutes); (2) Shift K^+ into cells: IV insulin (10 units) + dextrose; nebulized salbutamol; sodium bicarbonate if acidotic; (3) Remove K^+ from the body: loop diuretics if renal function present; sodium polystyrene sulphonate (Kayexalate) or patiromer (newer, better tolerated) orally; dialysis if severe or anuric. The dietitian's role: calculate all K^+ sources in nutrition support; adjust tube feed formula; review all medication K^+ content; counsel patients with CKD on dietary K^+ restriction.

PART FIVE — Chloride, Bicarbonate and Acid-Base Balance

Chloride is the primary extracellular anion, closely following sodium in most contexts. Bicarbonate is the primary buffer of the extracellular fluid and the key regulated variable in metabolic acid-base disorders. Together with the respiratory system (CO_2), they form the body's acid-base homeostasis system.

Acid-Base Physiology

The Henderson-Hasselbalch System and Clinical Disturbances

The Buffer Systems

The body maintains arterial pH between 7.35-7.45 through three overlapping buffer systems that operate on different timescales:

Buffer System	Reaction	Timescale	Clinical Significance
Bicarbonate- CO_2 (most important extracellular buffer)	$\text{CO}_2 + \text{H}_2\text{O} \rightleftharpoons \text{H}_2\text{CO}_3 \rightleftharpoons \text{H}^+ + \text{HCO}_3^-$ Regulated by lungs (CO_2) and kidneys (HCO_3^-)	Minutes (respiratory); hours to days (renal)	The primary clinical acid-base system. pH is determined by the ratio $\text{HCO}_3^-/\text{pCO}_2$ (not absolute values). Henderson-Hasselbalch: $\text{pH} = 6.1 + \log([\text{HCO}_3^-]/(0.03 \times \text{pCO}_2))$
Intracellular proteins and phosphates	Histidine residues on haemoglobin; intracellular phosphate groups accept or donate H^+	Seconds to minutes	Immediate buffering, particularly during acute changes. Haemoglobin buffers CO_2 in blood (Bohr effect).
Bone mineral buffers	Ca^{2+} , Na^+ , K^+ released from bone in exchange for H^+	Hours to days in chronic acidosis	Chronic metabolic acidosis (e.g., CKD) depletes bone mineral and contributes to osteoporosis. Dietary protein (acid-generating) vs. fruit/vegetable intake (base-generating) affects bone mineral preservation.

The Four Primary Acid-Base Disturbances

Disturbance	pH	Primary Change	Compensation	Common Causes	Nutritional Relevance
Metabolic acidosis	↓	$\text{HCO}_3^- \downarrow$	Respiratory: ↓ pCO_2 (Kussmaul breathing)	DKA; lactic acidosis (sepsis, hypoxia, metformin); diarrhoea (bicarbonate loss); renal tubular acidosis; CKD; starvation ketosis; salicylate poisoning	High-protein diets generate acid load. Diarrhoea causes direct HCO_3^- loss. Starvation generates ketoacid load. DKA: most common metabolic acidosis in nutritional practice.
Metabolic alkalosis	↑	$\text{HCO}_3^- \uparrow$	Respiratory: ↑ pCO_2 (hypoventilation, limited)	Vomiting (HCl loss); nasogastric suction; loop or thiazide diuretics; hypokalaemia (K^+ exits cells in exchange for H^+ ; H^+ enters cells); excess antacid use; post-hypercapnic alkalosis	Prolonged vomiting or NG suction in TPN patients. Diuretics in heart failure patients. Treat by replacing Cl^- (isotonic saline if volume-depleted) and K^+ .
Respiratory acidosis	↓	$\text{pCO}_2 \uparrow$	Renal: $\text{HCO}_3^- \uparrow$ (slow, days)	Hypoventilation: COPD, obesity hypoventilation, neuromuscular disease, opioid overdose, excessive carbohydrate feeding in ventilated patients	High CHO feeds generate more CO_2 per unit energy than fat; in ventilator-dependent patients, reducing carbohydrate and increasing fat can reduce pCO_2 and facilitate weaning
Respiratory alkalosis	↑	$\text{pCO}_2 \downarrow$	Renal: $\text{HCO}_3^- \downarrow$ (slow, days)	Hyperventilation: anxiety, pain, fever, sepsis (early), hypoxaemia, mechanical ventilation with excessive rate/volume; liver failure (ammonia stimulates respiratory centre)	Assess ventilator settings in mechanically ventilated patients; reduce respiratory drive by treating fever, pain, and anxiety; reduce CO_2 production by adjusting CHO/fat ratio

The Anion Gap — A Diagnostic Tool

Anion Gap (AG) = $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$. Normal range: 8–12 mEq/L. The 'gap' represents unmeasured anions (albumin, phosphate, sulphate, organic acids).

Anion Gap	What It Means	Common Causes
Elevated AG metabolic acidosis (>12)	Accumulation of unmeasured organic anions (ketoacids, lactic acid, uraemic anions) that consume HCO_3^-	MUDPILES mnemonic: Methanol; Uraemia (CKD); DKA; Propylene glycol; Isoniazid/Iron; Lactic acidosis; Ethylene glycol; Salicylates
Normal AG metabolic acidosis (<12)	Loss of HCO_3^- replaced by Cl^- (hyperchloraemic acidosis)	Diarrhoea (GI HCO_3^- loss); renal tubular acidosis; normal saline excess (dilutional, Cl^- loading); acetazolamide; ureteral diversion
Low AG	Reduced unmeasured anions	Hypoalbuminaemia (most common — each 1 g/dL fall in albumin lowers AG by ~2.5 mEq/L); multiple myeloma (abnormal positively-charged proteins)

CONNECT

Corrected anion gap for hypoalbuminaemia: In malnourished patients, the AG may appear normal even when organic anions are accumulating, because low albumin reduces the 'expected' anion gap. Always correct: Corrected AG = Calculated AG + $2.5 \times (4 - \text{albumin g/dL})$. This is clinically important in patients with malnutrition, liver disease, or nephrotic syndrome who are at risk of metabolic acidosis.

PART SIX — Clinical Application: Fluid and Electrolyte Issues in Nutritional Practice

The preceding physiology becomes immediately actionable in several common clinical nutrition scenarios. These are the situations where dietitians most frequently encounter and need to manage fluid and electrolyte concerns.

Clinical Nutrition Applications

Enteral Feeding, Parenteral Nutrition, GI Losses & Refeeding Syndrome

Refeeding Syndrome — The Most Dangerous Nutritional Electrolyte Emergency

Refeeding syndrome is the potentially fatal shift in fluids and electrolytes that occurs when nutrition is reintroduced to a malnourished patient. Understanding its mechanism is essential for every clinical dietitian.

WHY?

During prolonged starvation or severe restriction, cells adapt to a low-insulin, fat-burning state. When carbohydrates are reintroduced, insulin surges. Insulin drives potassium, phosphate, and magnesium from the bloodstream into cells (the cells need these to use the glucose for energy). The serum levels of these electrolytes fall precipitously — sometimes within hours of refeeding starting. The consequences can be fatal. This is not a hypothetical risk: refeeding deaths occur in anorexia nervosa patients, post-surgical patients, and chronically malnourished individuals.

Electrolyte Shift	Why It Happens	Consequence if Severe	Prevention/Management
Hypophosphataemia (most critical)	Phosphate is essential for ATP synthesis and for 2,3-DPG in red blood cells. Insulin-driven cellular uptake for glucose metabolism depletes plasma phosphate.	Serum $\text{PO}_4 < 0.5 \text{ mmol/L}$: respiratory failure (respiratory muscles fail); cardiac failure; haemolytic anaemia; encephalopathy; seizures; death. Even mild hypophosphataemia causes profound weakness.	Baseline phosphate $> 0.6 \text{ mmol/L}$ before starting feeds. If low, replace first. Monitor daily. Limit initial energy to 10 kcal/kg/day (or 50% of estimated requirements). Increase slowly over 5-7 days. IV phosphate if very low or oral not tolerated.
Hypokalaemia	Insulin drives K^+ into cells. Also, malnutrition causes total body K^+ depletion that is unmasked on refeeding.	Cardiac arrhythmias; respiratory muscle weakness; paralytic ileus; rhabdomyolysis	Check and normalise K^+ before starting feeds. Add K^+ to PN/enteral feeds from day 1. Monitor at least daily during first week.
Hypomagnesaemia	Same insulin-driven intracellular shift. Also, malnutrition causes total body Mg^{2+} depletion.	Refractory hypokalaemia (Mg^{2+} depletion causes K^+ renal wasting); cardiac arrhythmias; seizures; tetany	Always replace hypomagnesaemia. Refractory hypokalaemia that doesn't respond to K^+ alone $\rightarrow$ check Mg^{2+} and replace.
Sodium and fluid retention	Insulin causes renal Na^+ retention; carbohydrate feeding increases glycogen synthesis (glycogen is stored with water); intracellular Na^+ and water shift	Fluid overload, oedema, heart failure decompensation; particularly dangerous in patients with pre-existing cardiac or renal disease	Start with lower fluid volumes. Limit sodium in feeds initially. Monitor fluid balance, weight, and oedema daily.
Thiamin (B1) depletion	Thiamin is required for glucose metabolism via pyruvate dehydrogenase. Malnutrition depletes thiamin; refeeding with glucose rapidly consumes remaining thiamin.	Wernicke's encephalopathy (neurological emergency); high-output cardiac failure (wet beriberi)	Administer thiamin BEFORE starting feeds (100mg IV or IM). This is non-negotiable in any patient at risk of refeeding syndrome.

CAUTION

Who is at risk for refeeding syndrome? NICE criteria: HIGH RISK if any ONE of the following: BMI < 16 ; unintentional weight loss $> 15\%$ in last 3-6 months; little or no nutritional intake for > 10 days; low potassium, phosphate, or magnesium before refeeding. At MODERATE risk if any TWO of: BMI < 18.5 ; unintentional weight loss $> 10\%$; little or no intake > 5 days; alcohol misuse or drugs (insulin, antacids, diuretics). Risk populations: anorexia nervosa patients; patients post-prolonged ICU fasting; post-bariatric surgery; homeless or socially isolated individuals; prisoners; cancer patients on chemotherapy with poor intake.

Gastrointestinal Fluid Losses — What Is Lost and How to Replace It

GI Fluid Source	Volume/Day	Na ⁺ (mEq/L)	K ⁺ (mEq/L)	Cl ⁻ (mEq/L)	HCO ₃ ⁻ (mEq/L)	Clinical Consequence of Large Losses
Saliva	1.0-1.5 L	10	25	10	30	Usually reabsorbed in GI tract; significant only if unable to swallow or severe hypersalivation
Gastric juice	1.5-2.5 L	80	10	100	0 (acid)	Vomiting/NG suction: Na ⁺ and Cl ⁻ loss; HCl loss → metabolic alkalosis + hypokalaemia (secondary to alkalosis + aldosterone activation)
Pancreatic juice	1.0-2.0 L	130	10	75	115	Pancreatic fistula: massive HCO ₃ ⁻ and Na ⁺ loss → metabolic acidosis, volume depletion
Bile	0.5-1.0 L	145	5	100	25	Bile fistula or T-tube: Na ⁺ and Cl ⁻ loss; less acidosis than pancreatic fistula
Small intestinal fluid	1.0-3.0 L	115	5	100	20	High-output ileostomy (>1.5 L/day): major Na ⁺ , Cl ⁻ , and water loss; hyponatraemia and dehydration
Diarrhoea (secretory)	Variable (3-10+ L in cholera)	60-120	20-30	60-100	15-30	Na ⁺ and K ⁺ depletion; volume depletion; metabolic acidosis in severe cases (bicarbonate loss)

PRACTICE

For patients with high-output stomas, fistulae, or persistent diarrhoea: document output volume and character daily; estimate electrolyte losses using the table above; replace with electrolyte-containing fluids matched to what is being lost; ensure adequate Na⁺ in enteral feeds (high-output ileostomy patients often need additional sodium supplementation); check electrolytes 2-3 times per week. ORS (Oral Rehydration Solution) at Na⁺ 75-90 mEq/L is more appropriate for GI replacement than plain water, which worsens hyponatraemia in diarrhoeal losses.

Fluid and Electrolytes in Parenteral Nutrition

Parenteral nutrition provides all electrolytes intravenously, bypassing GI absorption. This requires precise calculation and daily monitoring because there is no physiological mechanism to prevent excess or correct deficiency through absorption regulation.

Electrolyte	Typical Adult PN Requirement	Key Adjustments	Common Errors
Sodium (Na ⁺)	1-2 mEq/kg/day (70-140 mEq/day)	Increase in high GI losses (fistula, NG suction); decrease in SIADH, fluid retention, heart failure; adjust based on serum Na ⁺	Too much Na ⁺ in oedematous patients (heart failure, cirrhosis); too little in patients with high output losses
Potassium (K ⁺)	1-2 mEq/kg/day (70-140 mEq/day)	Increase in high output losses, diuretic use, alkalosis, refeeding; decrease in renal impairment, ACE inhibitors, hyperkalaemia	Insufficient K ⁺ in refeeding patients; excess in CKD patients; failure to monitor and adjust daily
Phosphate (PO ₄ ³⁻)	20-40 mmol/day	Significantly increase in refeeding syndrome (30-60 mmol/day); reduce in CKD (phosphate restriction)	Most commonly under-supplemented during refeeding; catastrophic outcomes possible
Magnesium (Mg ²⁺)	8-20 mEq/day (1-2.5 g/day as MgSO ₄)	Increase in malabsorption, diarrhoea, diuretic use, refeeding; check and correct hypomagnesaemia before addressing hypokalaemia	Forgotten in the face of more dramatic electrolyte abnormalities; causes refractory hypokalaemia if depleted
Calcium (Ca ²⁺)	10-15 mEq/day (as gluconate in PN)	Cannot mix with phosphate in same IV solution (precipitates) — must use separate infusion or lipid-protected 3-in-1 formulation	CaHPO ₄ precipitation in PN bag — can cause pulmonary embolism if infused; pharmacist solubility calculation required
Chloride and acetate	Adjusted to maintain acid-base balance	More Cl ⁻ if alkalosis (metabolic alkalosis: need Cl ⁻ to replace HCO ₃ ⁻); more acetate (metabolised to HCO ₃ ⁻) if acidosis	Fixed Cl ⁻ ratios in stock PN formulas may not match patient's acid-base status

Hydration Assessment and Requirements

Fluid requirements vary considerably by patient, condition, and environment. The following framework provides starting estimates that must always be adjusted based on clinical assessment.

Method	Formula	Notes and Limitations
Weight-based (most common)	25-35 mL/kg/day for adults (30 mL/kg/day is the standard starting point)	Use lower end (25-30 mL/kg) for older adults, heart failure, renal impairment; higher end (30-35 mL/kg) for fever, high GI output, hot environment

Holliday-Segar (paediatric)	100 mL/kg for first 10 kg; + 50 mL/kg for 10-20 kg; + 20 mL/kg above 20 kg	Provides daily maintenance for children; adjust for fever (+12% per degree above 37.5°C), burns, GI losses
Energy-based	1 mL/kcal for adults; 1.5 mL/kcal for infants	Simple but requires accurate energy estimation; useful for enteral formula planning
Urine output monitoring	Target urine output >0.5 mL/kg/hour (adults); >1 mL/kg/hour (children)	Most sensitive indicator of adequate hydration. Urine specific gravity >1.020 suggests concentrated urine and relative dehydration. Not applicable in patients with renal failure or diuretic use.

CONTEXT

In hot climates (Sudan, Sahel region, Middle East), ambient temperature significantly increases insensible water losses from sweating. At 35-40°C with physical activity, sweat losses can reach 1-2 litres per hour. This increases daily fluid requirements dramatically, particularly for outdoor workers, soldiers, pilgrims (Hajj), and people without air conditioning. Standard 30 mL/kg/day recommendations are inadequate for these populations. Sports drink and ORS electrolyte replacement becomes important because plain water ingestion in large volumes without sodium replenishment causes exercise-associated hyponatraemia (EAH), which has caused deaths in endurance athletes and military personnel.

Clinical Scenario: Integrated Case: Amira, 22 Years Old, University Student, Khartoum

- Amira is a 22-year-old university student with anorexia nervosa who has been restricting her intake for 18 months. She has lost 22% of her body weight (BMI 14.8). She presents acutely to the hospital emergency department after collapsing at home. On admission: BP 85/55 mmHg lying, unable to stand; HR 115 bpm; temperature 36.2°C. She is confused and lethargic. Blood results: Na⁺ 128 mEq/L; K⁺ 2.8 mEq/L; Cl⁻ 88 mEq/L; HCO₃⁻ 32 mEq/L; phosphate 0.45 mmol/L; magnesium 0.55 mmol/L; albumin 24 g/L; glucose 3.1 mmol/L; haemoglobin 9.2 g/dL.
- Question 1: Identify the fluid and electrolyte disturbances present. For each abnormal value, explain the likely mechanism that produced it in the context of Amira's clinical presentation.
- Question 2: Calculate her anion gap. Interpret the acid-base status. What type of acid-base disturbance is present, and why? What are the primary causes in her situation?
- Question 3: The medical team wants to start enteral nutrition immediately via nasogastric tube. What are the refeeding syndrome risks specific to Amira? What must be done before feeding is started, and what should the initial feeding prescription look like?
- Question 4: Over the first 48 hours of careful refeeding, her phosphate drops to 0.28 mmol/L and she becomes severely breathless. Explain the mechanism of this complication and the immediate clinical response required.
- Question 5: After 2 weeks, Amira's feeding is progressing. Her serum Na⁺ has corrected to 136 mEq/L but she developed generalized oedema on day 4 of refeeding. Her family asks why she is swelling when she is eating again. Explain the mechanism of refeeding oedema and when it typically resolves.

Critical Thinking Questions

- The principle that 'the body sacrifices osmolarity to preserve volume' explains why hyponatraemia is common in volume-depleted states even though the deficit should logically cause hypernatraemia. How does this principle change your approach to managing hyponatraemia — and when is treating the sodium itself inadequate?
- Refeeding syndrome electrolyte shifts can be fatal, yet the treatment is simple: start slowly, replace electrolytes before and during refeeding, and give thiamin. Despite this, refeeding deaths continue to occur. What systemic, educational, or practice-level factors contribute to this preventable complication continuing to happen — and what role can dietitians play in reducing it?
- In hot-climate settings like Sudan, sports and physical activity carry real risk of exercise-associated hyponatraemia (from drinking plain water without sodium) as well as hypernatraemic dehydration (from inadequate fluid intake). These seem contradictory but are both common. How would you design a simple, culturally appropriate hydration message for (a) athletes, (b) manual labourers, and (c) children in an outdoor school setting?

Lecture Summary — Key Takeaways for Dietetic Practice

- Body fluid compartments: ICF (40% BW, K^+ -dominant) and ECF (20% BW, Na^+ -dominant) separated by osmotic forces at cell membranes; intravascular and interstitial separated by Starling forces (oncotic vs hydrostatic). Water moves passively following solutes — every fluid disturbance is ultimately about altered solute distribution.
- Water regulation: ADH (released by hypothalamic osmosensors at >295 mOsm/kg) causes renal water retention. Volume depletion overrides osmolarity — causing water retention even when serum Na^+ is already low. SIADH (inappropriate ADH secretion) causes euvolaemic hyponatraemia; treat with fluid restriction and address underlying cause.
- Sodium: primary ECF osmole and volume determinant. Hyponatraemia classified by volume status — hypovolaemic (GI/renal losses), euvolaemic (SIADH, polydipsia), hypervolaemic (heart failure, cirrhosis). Correction rate matters: max 8-10 mEq/L per 24h for chronic hyponatraemia to prevent osmotic demyelination. Hypernatraemia always means water deficit — look for inadequate intake, DI, hypotonic losses.
- Potassium: primary ICF cation; sets membrane potential. Hypokalaemia (weakness, arrhythmias) — treat K^+ AND Mg^{2+} (refractory hypokalaemia without Mg replacement). Hyperkalaemia (peaked T waves, cardiac arrest) — acute management: calcium, insulin+dextrose, kayexalate/dialysis. Acid-base connection: acidosis raises K^+ ; alkalosis lowers K^+ ; DKA has total body K^+ depletion masked by acidosis.
- Acid-base: pH maintained 7.35-7.45 by bicarbonate buffer system (regulated by lungs for pCO_2 and kidneys for HCO_3^-). Four disturbances: metabolic acidosis (low HCO_3^- — DKA, diarrhoea, CKD, lactic acidosis); metabolic alkalosis (high HCO_3^- — vomiting, diuretics); respiratory acidosis (high pCO_2 — COPD, high-CHO feeds in ventilated patients); respiratory alkalosis (low pCO_2 — anxiety, sepsis, fever). Anion gap helps classify metabolic acidosis; correct for albumin.

- Clinical nutrition applications: Refeeding syndrome — give thiamin before starting feeds; begin at 10 kcal/kg/day; monitor phosphate, K^+ , Mg^{2+} daily and supplement pre-emptively. GI fluid losses — match replacement to what is lost (gastric losses: Cl^- -rich, alkalinizing; pancreatic/intestinal: HCO_3^- -rich, acidifying; diarrhoea: Na^+ and K^+ -rich). PN electrolytes — individualize daily; can't mix Ca^{2+} and phosphate directly; use acetate vs chloride to correct acid-base. Fluid requirements: 25-35 mL/kg/day but adjust for hot climate, fever, GI losses, cardiac/renal disease.

Suggested reading:

1. Rose BD & Post TW (2001). Clinical Physiology of Acid-Base and Electrolyte Disorders, 5th Ed. McGraw-Hill — the definitive clinical reference. |
2. NICE Clinical Guideline CG32 (2006, updated 2017): Nutrition support for adults: oral nutrition support, enteral tube feeding and parenteral nutrition — includes refeeding syndrome criteria and management. |
3. Mehanna HM et al. (2008). Refeeding syndrome: what it is, and how to prevent and treat it. BMJ.
4. Sterns RH (2015). Disorders of plasma sodium. NEJM. |
5. Kraft MD et al. (2005). Treatment of electrolyte disorders in adult patients in the intensive care unit. American Journal of Health-System Pharmacy.

List of Abbreviations

All abbreviations used in the lecture, alphabetically ordered

MS Nutrition & Dietetics Program | Body Regulation: Fluids & Electrolytes

This list includes every abbreviation, acronym, symbol, and shorthand used in the Fluids & Electrolytes lecture. Entries are arranged alphabetically. Ion symbols (Na^+ , K^+ , etc.) and chemical formulae are grouped at the end of the list.

Abbreviation	Full Term and Explanation
ACE	Angiotensin-Converting Enzyme — the enzyme that converts angiotensin I to angiotensin II; inhibited by ACE inhibitor medications (e.g., enalapril, lisinopril), which reduce aldosterone and can cause hyperkalaemia
ADH	Antidiuretic Hormone (also called Vasopressin) — the hormone secreted by the posterior pituitary that causes water retention in the renal collecting duct
AG	Anion Gap — calculated as $[\text{Na}^+] - ([\text{Cl}^-] + [\text{HCO}_3^-])$; used to classify the cause of metabolic acidosis
ARB	Angiotensin Receptor Blocker — medication class that blocks the angiotensin II receptor; similar effect to ACE inhibitors on potassium
ATP	Adenosine Triphosphate — the primary energy currency of the cell; requires phosphate and magnesium for synthesis
BMI	Body Mass Index — weight (kg) divided by height squared (m^2); used in refeeding syndrome risk criteria
BP	Blood Pressure
BUN	Blood Urea Nitrogen — a measure of urea in blood; used in the estimated serum osmolality formula; elevated in dehydration and renal disease
BW	Body Weight
CHO	Carbohydrate — used throughout the acid-base section (e.g., high-CHO feeds increase CO_2 production)
CKD	Chronic Kidney Disease — progressive loss of renal function; impairs potassium excretion, acid-base regulation, phosphate balance, and fluid management

CNS	Central Nervous System — brain and spinal cord; CNS disorders are a major cause of SIADH
COPD	Chronic Obstructive Pulmonary Disease — common cause of chronic respiratory acidosis (CO ₂ retention)
CSF	Cerebrospinal Fluid — transcellular fluid surrounding the brain and spinal cord
DI	Diabetes Insipidus — disorder of water regulation due to absent (central DI) or non-responsive (nephrogenic DI) ADH; causes massive dilute urine output and hypernatraemia
DKA	Diabetic Ketoacidosis — life-threatening complication of diabetes characterized by elevated anion gap metabolic acidosis from ketoacid accumulation; causes total body potassium depletion masked by acidosis-driven extracellular shift
DPG	2,3-Diphosphoglycerate — compound in red blood cells that regulates oxygen release from haemoglobin; synthesis requires adequate phosphate
EAH	Exercise-Associated Hyponatraemia — dangerous fall in serum sodium caused by drinking excessive plain water during endurance exercise without sodium replacement
ECF	Extracellular Fluid — all body fluid outside cells (~14 litres in a 70 kg adult); dominant cation is Na ⁺ ; subdivided into intravascular (plasma) and interstitial fluid
ENaC	Epithelial Sodium Channel — the principal apical channel through which sodium enters tubular cells in the collecting duct; regulated by aldosterone
GFR	Glomerular Filtration Rate — measure of kidney filtering capacity (mL/min); used to stage CKD; GFR <30 significantly impairs potassium and phosphate excretion
GI	Gastrointestinal — relating to the stomach and intestines; GI fluid losses (vomiting, diarrhoea, fistulae, high-output stoma) are a major cause of fluid and electrolyte disturbances
HCl	Hydrochloric acid — the acid secreted by gastric parietal cells; its loss in vomiting causes metabolic alkalosis and hypochloraemia
HR	Heart Rate
ICF	Intracellular Fluid — all body fluid inside cells (~28 litres in a 70 kg adult); dominant cation is K ⁺ ; also contains Mg ²⁺ and organic phosphates
ICU	Intensive Care Unit
IM	Intramuscular — route of injection; e.g., thiamin given IM before refeeding is started
IV	Intravenous — route of administration directly into a vein; used for fluid replacement, electrolyte supplementation, and parenteral nutrition

JVP	Jugular Venous Pressure — clinical estimate of central venous pressure; low JVP indicates volume depletion; elevated JVP suggests fluid overload or right heart failure
mEq	Milliequivalent — unit of electrolyte concentration accounting for valence (charge); used for monovalent ions like Na^+ , K^+ , Cl^- , HCO_3^-
mmol	Millimole — unit of amount; used interchangeably with mEq for monovalent ions; preferred for divalent ions like phosphate, calcium, magnesium
mOsm	Milliosmole — unit of osmotic concentration; normal serum osmolality is 275–295 mOsm/kg
NaCl	Sodium chloride (isotonic saline) — 0.9% NaCl = 'normal saline'; used for volume replacement; excess can cause hyperchloraemic metabolic acidosis
NG	Nasogastric — relating to a tube passing through the nose into the stomach; NG suction removes gastric acid and can cause metabolic alkalosis and electrolyte depletion
NICE	National Institute for Health and Care Excellence (UK) — the body that publishes the clinical guidelines referenced for refeeding syndrome criteria
NSAID	Non-Steroidal Anti-Inflammatory Drug — medication class (e.g., ibuprofen, diclofenac) that inhibits prostaglandin synthesis; reduces renal blood flow and can impair K^+ excretion, worsen CKD, and cause fluid retention
ODS	Osmotic Demyelination Syndrome — severe neurological complication caused by overly rapid correction of chronic hyponatraemia; previously called central pontine myelinolysis; can cause permanent paralysis
ORS	Oral Rehydration Solution — glucose-electrolyte solution (WHO formula: Na^+ 75 mEq/L, K^+ 20 mEq/L, glucose 75 mmol/L, citrate 10 mEq/L) used to treat and prevent dehydration from diarrhoeal illness; exploits SGLT1 co-transport of glucose and sodium
PEEP	Positive End-Expiratory Pressure — a ventilator setting that keeps airways open at end of expiration; can cause ADH release by reducing venous return and triggering volume-sensing reflexes
pH	Measure of hydrogen ion concentration in solution; physiological range 7.35–7.45; <7.35 is acidaemia, >7.45 is alkalaemia
PN	Parenteral Nutrition — intravenous administration of all nutrients (glucose, amino acids, lipids, electrolytes, vitamins, minerals)
RAAS	Renin-Angiotensin-Aldosterone System — hormonal cascade activated by low blood pressure or low sodium delivery to the kidney; produces angiotensin II (vasoconstriction) and aldosterone (sodium retention, potassium excretion)

ROMK	Renal Outer Medullary Potassium channel — the potassium channel in the apical membrane of collecting duct principal cells through which K^+ is secreted into urine; regulated by aldosterone; inhibited by hypomagnesaemia
SGLT1	Sodium-Glucose Linked Transporter 1 — the co-transporter in small intestinal enterocytes that absorbs glucose and sodium together; the mechanism exploited by ORS (glucose drives Na^+ absorption even in secretory diarrhoea)
SIADH	Syndrome of Inappropriate Antidiuretic Hormone Secretion — condition in which ADH is continuously secreted without appropriate osmotic or volume stimuli, causing water retention, euvoaemic hyponatraemia, and inappropriately concentrated urine
SNRI	Serotonin-Norepinephrine Reuptake Inhibitor — antidepressant medication class; a cause of SIADH
SSRI	Selective Serotonin Reuptake Inhibitor — antidepressant medication class (e.g., fluoxetine, sertraline); the most commonly encountered drug cause of SIADH in outpatients
TB	Tuberculosis — pulmonary TB listed as a cause of SIADH through pulmonary mechanisms
TBW	Total Body Water — approximately 60% of body weight in adults (~42 litres in a 70 kg adult); divided into ICF (2/3) and ECF (1/3)
TPN	Total Parenteral Nutrition — complete nutritional support delivered intravenously; synonym for PN; 'total' emphasises that all nutrients are provided parenterally without any enteral input
V2	Vasopressin receptor subtype 2 — the ADH receptor on renal collecting duct principal cells; its activation causes insertion of aquaporin-2 water channels, increasing water permeability and reabsorption
WBC	White Blood Cell (leukocyte) — very high white cell count can cause pseudohyperkalaemia by releasing intracellular K^+ when blood clots in the collection tube
WHO	World Health Organization — the United Nations health agency; the 2002 WHO ORS formula (reduced-osmolality) is referenced in the lecture
Ca^{2+}	Calcium ion — divalent cation; 99% in bone; ECF Ca^{2+} regulated by PTH, calcitriol, and calcitonin; required for muscle contraction, coagulation, and nerve signaling
Cl^-	Chloride ion — primary extracellular anion; closely follows sodium; lost in vomiting (as HCl); used in the anion gap formula
CO_2	Carbon Dioxide — gaseous form of carbonic acid; regulated by the lungs; key variable in respiratory acid-base disturbances
CO_2	Carbon dioxide

H⁺	Hydrogen ion (proton) — the acid; its concentration determines pH; exchanged with K ⁺ across cell membranes in acid-base disturbances
H₂CO₃	Carbonic acid — the intermediate formed when CO ₂ dissolves in water; rapidly equilibrates with H ⁺ + HCO ₃ ⁻ via carbonic anhydrase
H₂O	Water
HCO₃⁻	Bicarbonate ion — the primary extracellular buffer; produced by the kidneys; its ratio to pCO ₂ determines blood pH; low in metabolic acidosis, high in metabolic alkalosis
HPO₄²⁻	Hydrogen phosphate ion — one form of phosphate in solution; part of the phosphate buffer system
K⁺	Potassium ion — primary intracellular cation; sets resting membrane potential; regulated by aldosterone and insulin
Mg²⁺	Magnesium ion — predominantly intracellular; cofactor for >300 enzymes; required for K ⁺ renal retention; depleted in refeeding syndrome
Na⁺	Sodium ion — primary extracellular cation; determines ECF osmolality and volume; regulated by aldosterone and ADH
pCO₂	Partial pressure of carbon dioxide — the respiratory component of acid-base balance; regulated by breathing rate and depth; elevated in respiratory acidosis, reduced in respiratory alkalosis

Note: Subscript and superscript notation used throughout (e.g., HCO₃⁻, Ca²⁺) follows standard biochemistry convention. The lecture also uses standard SI units: mEq/L (milliequivalents per litre) for electrolyte concentrations, mmol/L (millimoles per litre) for phosphate, calcium, magnesium and glucose, and mOsm/kg (milliosmoles per kilogram) for osmolality.

Module 2 — Body Regulation & Composition

Internal Balance & Physical Assessment

Internal Balance & Physical Assessment

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Body Composition

Models, Lifespan Changes, Measurement Techniques & Clinical Assessment

- ▶ Part 1: Body Composition Models — 2C, 3C & 4C Frameworks
- ▶ Part 2: Assessment Methods — Anthropometry | BIA | DEXA | ADP | CT/MRI/Ultrasound
- ▶ Part 3: Adiposity — VAT, SAT, Ectopic Fat & the Adipokine Profile
- ▶ Part 4: Sarcopenia — EWGSOP2 Criteria, Mechanisms & Nutritional Management
- ▶ Part 5: BMI — Legitimate Uses & Systematic Limitations
- ▶ Part 6: Special Populations — Malnutrition | Athletes | Older Adults
- ▶ Clinical Case: Three Women, One BMI — Body Composition Phenotypes

Body Composition

Assessment Methods, Fat Mass vs. Fat-Free Mass, Adiposity, Sarcopenia & Clinical Application

Focus: What the body is made of, why it matters clinically, and how to measure it accurately

Why Body Composition Matters: Beyond the Scale

Body weight tells us very little on its own. Two people of identical weight, height, sex, and age can have dramatically different health profiles — one with 35% body fat and sarcopenic muscle mass, the other with 20% fat and robust lean tissue. The number on the scale cannot tell us which is which. Body composition assessment — quantifying the relative proportions of fat mass, muscle, bone, and water — is the tool that transforms weight into clinically actionable information.

WHY?

In clinical nutrition practice, the core questions are not 'how much does this patient weigh?' but 'how much muscle do they have?', 'how much fat, and where is it located?', 'are they losing muscle or fat?', and 'how does their body composition relate to their disease risk and treatment outcomes?'. This lecture builds the conceptual and technical foundation to answer these questions with rigor.

Learning Outcomes — By the end of this lecture, students will be able to:

- Define the major body composition models (two-compartment, four-compartment) and explain what each measures and why models matter
- Describe the major methods of body composition assessment (BIA, anthropometry, DEXA, ADP, underwater weighing), explain their principles, accuracy, and appropriate clinical use
- Explain the roles of fat mass, visceral adipose tissue, and subcutaneous adipose tissue in metabolic disease risk
- Define sarcopenia and explain its mechanisms, clinical consequences, and assessment criteria
- Connect BMI limitations to body composition reality and explain when BMI is and is not a useful clinical tool
- Apply body composition assessment concepts to clinical scenarios: obesity, malnutrition, ageing, athletic populations, and disease states

PART ONE — What Is Body Composition? The Modelling Framework

Body composition refers to the quantitative description of what the human body is made of. Because the body cannot be directly dissected in vivo, we use models — conceptual frameworks that partition body mass into components that can be measured or estimated. The model chosen determines what is measured and how results should be interpreted.

Body Composition Models

From Two Compartments to Molecular Components

Model	Compartments	What It Measures	Key Assumptions & Limitations
Two-Compartment (2C) Model	Fat Mass (FM) Fat-Free Mass (FFM)	Divides total body mass into fat and everything else (FFM = muscle + bone + water + organs)	Assumes FFM has constant density (1.1 g/mL) and constant water content (73%). These assumptions are violated in oedema, dehydration, ageing, children, athletes, and ethnic groups. Most field methods (hydrodensitometry, BIA, skinfolds) use 2C models and inherit these errors.
Three-Compartment (3C) Model	Fat Mass Bone Mineral Content Fat-Free Soft Tissue	Separates bone mineral from the soft tissue FFM	Requires DEXA to measure bone mineral separately. Reduces errors from variation in bone density (relevant in osteoporosis, athletes, the elderly).
Four-Compartment (4C) Model — gold standard	Fat Mass Bone Mineral Total Body Water Residual protein/other	Separates fat, water, bone mineral, and protein mass independently	Most accurate model because it accounts for variation in FFM density. Requires multiple measurements (hydrodensitometry or ADP + DEXA + isotope dilution). Research standard, rarely practical in routine clinical settings.
Five- or Six-Compartment (Molecular Model)	Fat, water, protein, mineral, glycogen (+ individual organs)	Used in research and detailed body composition studies	Requires multiple reference methods simultaneously. Used primarily in research to validate simpler field methods.

WHY?

Understanding the model matters for interpreting results. When a bioelectrical impedance scale tells a patient their fat percentage has dropped by 5% overnight, this is almost certainly a measurement artefact from change in hydration status — not a real fat loss. The BIA model assumes constant hydration of FFM; when that assumption is violated (dehydration, oedema, recent meal, exercise), the fat estimate changes even though actual fat has not changed. Every body composition method has built-in assumptions, and every result must be interpreted in that light.

Fat Mass vs. Fat-Free Mass: The Two Fundamental Compartments

Compartment	Definition	Subcomponents	Clinical Significance
Fat Mass (FM)	All extractable lipid in the body: triglycerides in adipose tissue, phospholipids in cell membranes, lipids in the central nervous system	Essential fat (~3-5% in men, 10-13% in women): structural lipids in cell membranes, CNS myelin, hormonal fat; Storage fat: adipose tissue triglycerides — the variable component that changes with energy balance	Too high: obesity-related metabolic risk. Too low: hormonal disruption (loss of menstrual cycle in female athletes and anorexia nervosa), impaired fat-soluble vitamin storage, immune dysfunction.
Fat-Free Mass (FFM)	Everything that is not fat: water (~73%), protein (~20%), mineral (~7%), glycogen (~1%)	Skeletal muscle (largest component of FFM, ~40-50% of body weight in healthy adults); Bone mineral; Organs (liver, kidney, heart, brain); Extracellular water (plasma, interstitial)	FFM is the metabolically active mass. It determines basal metabolic rate (~70-80% of BMR). Low FFM = low BMR, poor functional capacity, immune impairment. Skeletal muscle is the primary site of glucose disposal and amino acid reservoir for immune and repair functions.
Lean Body Mass (LBM)	Similar to FFM but includes essential fat (~3% in men, 12% in women); used inconsistently in the literature	Includes the structural fat that cannot be eliminated without physiological harm	Often used interchangeably with FFM in clinical practice, though technically different. Clarify which is being used when interpreting body composition reports.

PART TWO — Methods of Body Composition Assessment

No single method measures all compartments directly. Each method estimates one or more components from measurable proxies (electrical resistance, X-ray attenuation, buoyancy, sound, imaging). Understanding the principle behind each method is essential for selecting the right tool and interpreting results appropriately.

Assessment Methods

From Skinfold Calipers to DEXA — Principles, Accuracy and Clinical Use

1. Anthropometry — The Accessible Field Method

Anthropometry (from Greek: 'measurement of the human') uses simple physical measurements to estimate body composition and assess nutritional status. It is the most widely accessible method globally and the primary tool in clinical nutrition assessment in resource-limited settings.

Measurement	What It Estimates	Method	Clinical Use & Limitations
Body Mass Index (BMI)	Crude proxy for adiposity in populations	Weight (kg) / Height (m) ²	Simple, reproducible, widely used for population-level screening. Significant limitations: does not distinguish fat from muscle; does not identify fat distribution; misclassifies ~30-40% of individuals (athletic individuals over-classified as overweight; sarcopenic obese individuals under-classified as normal). Ethnic-specific cut-offs needed (Asian populations have higher metabolic risk at lower BMI thresholds: overweight ≥ 23 , obese ≥ 27.5).
Waist Circumference (WC)	Central/abdominal adiposity	Measured at the midpoint between lower rib and iliac crest (WHO method) or at the level of the umbilicus (alternative)	Better predictor of metabolic risk and visceral fat than BMI. Risk thresholds: >102 cm men / >88 cm women (North American); >90 cm men / >80 cm women (Asian/South Asian). Serial measurement valuable for monitoring intervention response.
Waist-to-Hip Ratio (WHR)	Fat distribution pattern (android vs gynoid)	WC / Hip circumference	Distinguishes 'apple-shaped' (android, visceral) from 'pear-shaped' (gynoid, peripheral) fat distribution. High risk: >0.90 men, >0.85 women. Less commonly used now that WC alone is validated as a risk predictor.
Waist-to-Height Ratio (WHtR)	Central adiposity adjusted for height	WC / Height	A single cut-off of 0.5 ('keep your waist to less than half your height') applies across different ethnic groups and both sexes; stronger predictor of cardiometabolic risk than BMI across populations.

Skinfold Thickness	Subcutaneous fat thickness at specific sites	Caliper at 4 sites (biceps, triceps, subscapular, suprailiac) — Durnin & Womersley equations; or 7-site protocol (Jackson & Pollock)	Estimates total body fat % via regression equations. Accuracy depends heavily on technique standardization and the appropriateness of the reference equations for the population (most equations validated in young, White Western adults). Error ± 3 -5% body fat in skilled hands; ± 8 -10% with poor technique. Not appropriate for obese patients or for populations differing from validation samples.
Mid-Upper Arm Circumference (MUAC)	Muscle + fat at mid-upper arm; proxy for lean mass	Tape measure at midpoint of left upper arm	Primary rapid-assessment tool for acute malnutrition in children and adults in field settings (UNHCR, WHO, MSF). MUAC <125 mm: severe acute malnutrition in children; <185 mm: adults at risk. Serial measurements track muscle wasting. Widely used in Sudan and conflict-affected settings.
Calf Circumference	Muscle mass proxy in older adults	Tape at widest point of calf	Validated as a simple sarcopenia screening tool: <31 cm associated with low muscle mass in adults >60 years. Easy, non-invasive, useful in bedside assessment of muscle wasting in elderly patients.

CONTEXT

MUAC in Sudan and humanitarian settings: Mid-Upper Arm Circumference is the primary field tool for nutritional assessment across Sudan, the Sahel, and humanitarian crisis settings. It requires no weight or height measurement, is fast, cheap, and predicts mortality risk in acute malnutrition independently of other measures. UNHCR and WFP use MUAC as the primary admission and discharge criterion for therapeutic feeding programs. A MUAC tape colored yellow (<230 mm, moderate risk), orange (<210 mm, at-risk), and red (<125 mm in children, severe acute malnutrition) enables rapid community-level screening by health workers with minimal training. MUAC-based admission criteria have been shown to identify different children from those identified by weight-for-height z-score alone, suggesting the two approaches are complementary.

2. Bioelectrical Impedance Analysis (BIA)

BIA passes a small, painless alternating electrical current through the body and measures the resistance (impedance) to that current. Because fat-free mass (which contains water and electrolytes) conducts electricity well while fat mass does not, the measured impedance can be used to estimate total body water and, from that, fat-free mass and fat mass.

BIA Type	Principle	Accuracy	Best Clinical Use
Single-frequency BIA (SF-BIA) 50 kHz	One frequency measures total body water; FFM estimated via population equations	Moderate accuracy (± 3 -5% body fat vs 4C model); heavily assumption-dependent	Routine clinical monitoring of nutritional support; population-level screening. Avoid in: oedema, dehydration, recent vigorous exercise,

			extreme BMI (<16 or >40).
Multi-frequency BIA (MF-BIA)	Multiple frequencies (1-500 kHz) distinguish intra- and extracellular water	Better than SF-BIA; estimates extra- and intra-cellular fluid separately	More accurate fluid status assessment; useful in CKD, heart failure, ICU fluid monitoring
Bioelectrical Impedance Spectroscopy (BIS)	Full frequency spectrum; uses Cole-Cole modelling to separate ICW and ECW	Good accuracy for fluid compartments; limited body fat accuracy	ICU and renal patients: fluid overload detection; dry weight estimation in dialysis
Segmental BIA	Measures each limb and trunk separately	Better than whole-body for detecting regional muscle wasting	Detecting limb-specific muscle wasting; sarcopenia screening
Phase Angle (PA)	Ratio of reactance to resistance; reflects cell membrane integrity and hydration	Validated prognostic marker (not a compositional measure)	Lower PA predicts worse outcomes in cancer, liver disease, HIV, and critical illness. Normal $\geq 5^\circ$ in adults; $< 4^\circ$ indicates severe nutritional depletion and poor prognosis.

CAUTION

BIA standardization requirements: Results are highly sensitive to hydration status, recent food intake, physical activity, bladder fullness, skin temperature, and electrode placement. Standardized conditions must be enforced for meaningful serial measurements: (1) fasted for at least 4 hours; (2) no strenuous exercise for 12 hours; (3) voided bladder immediately before; (4) no alcohol for 24 hours; (5) supine for 5-10 minutes before measurement; (6) consistent electrode placement. In clinical settings, these conditions are rarely met — single BIA measurements should be interpreted cautiously; trends over time with consistent conditions are more reliable than single values.

3. Dual-Energy X-ray Absorptiometry (DEXA/DXA)

DEXA uses two X-ray beams at different energy levels to differentiate soft tissue from bone mineral. Because fat and lean soft tissue attenuate X-rays differently, DEXA can partition the body into three compartments: fat mass, lean soft tissue (approximately muscle + organs), and bone mineral content. It is currently the most widely used clinical reference method.

Characteristic	Detail
Principle	Two X-ray beams (70 and 140 keV) are differentially attenuated by fat, lean tissue, and bone mineral; software reconstructs regional and total body composition
Accuracy vs. 4C model	Overestimates fat mass in dehydrated patients; underestimates in oedematous patients; variation between manufacturers (Hologic vs GE Lunar — results not directly comparable); errors of ~1-2 kg fat mass vs 4C model
Advantages	Regional analysis: can separately measure trunk, arm, leg, android, gynoid fat; visceral fat estimation (via android/gynoid ratio and trunk fat); bone mineral density (BMD) simultaneously; radiation dose very low (~1-6 μ Sv, < 1 day background radiation)
Limitations	Cannot accommodate patients >160 kg or >190 cm width; affected by hydration status and glycogen content; scan tables have weight limits; expensive; not portable; radiation (minor but present; not used in pregnant women or for frequent serial measurements)
Clinical use	Gold standard for longitudinal body composition monitoring; sarcopenia diagnosis (appendicular lean mass index); visceral fat estimation; bone mineral density in osteoporosis assessment; obesity phenotyping; evaluating body composition response to nutritional interventions
Appendicular Lean Mass Index (ALMI)	$(\text{Arm lean mass} + \text{Leg lean mass}) / \text{Height}^2$; the primary DEXA-derived metric for sarcopenia diagnosis. Low ALMI: <7.0 kg/m ² in men, <5.5 kg/m ² in women (EWGSOP2 criteria)

4. Air Displacement Plethysmography (ADP) — the Bod Pod

ADP measures body volume by the air displaced when a person sits inside a sealed chamber (the Bod Pod). Body density is calculated from body mass and volume. Fat mass and fat-free mass are estimated using the same two-compartment density equations as hydrodensitometry, but without water immersion.

- Principle: Body volume = Volume of empty chamber – Volume with person inside (measured by pressure changes). Density = Mass ÷ Volume. Fat % from Siri equation: %Fat = $(4.95/\text{Density} - 4.50) \times 100$.
- Advantages over hydrodensitometry: No water immersion required; faster (5-10 minutes); tolerated by elderly, children, obese, and those with physical limitations; good test-retest reliability.
- Accuracy: Comparable to hydrodensitometry; ± 2 -3% body fat vs 4C model in most populations. Lung volume correction required (residual volume must be measured or estimated — estimation introduces error).
- Limitations: Expensive; not portable; body hair and loose clothing trap air (must wear tight swimsuit and swim cap); affected by recent food/fluid intake and surface temperature.

5. Imaging Methods: CT, MRI, Ultrasound

Method	What It Measures	Key Advantage	Key Limitation
CT (Computed Tomography)	Cross-sectional areas of fat (visceral vs subcutaneous) and muscle at specific anatomical levels (typically L3 vertebra)	Gold standard for visceral adipose tissue (VAT) quantification; distinguishes VAT from subcutaneous AT (SAT) precisely; muscle cross-sectional area; identifies ectopic fat (intrahepatic, intramuscular)	High radiation; expensive; not portable; single-slice measurement extrapolated to whole body; operator-dependent segmentation. L3 cross-sectional muscle area is the reference standard for skeletal muscle index in sarcopenia research.
MRI (Magnetic Resonance Imaging)	Same as CT but radiation-free; full-body fat and muscle compartment analysis possible	No radiation; excellent soft tissue contrast; can image whole-body fat distribution; used in paediatric and pregnant populations; detects ectopic fat (liver, pancreas, heart, muscle)	Expensive; not portable; long scan time; claustrophobia; not suitable for patients with metal implants; contraindicated in some cardiac devices
Ultrasound	Muscle thickness and cross-sectional area; subcutaneous fat layer thickness; muscle echo intensity (reflects intramuscular fat/fibrosis)	Portable; radiation-free; bedside use; real-time; relatively inexpensive; suitable for ICU and field settings	Operator-dependent; 2D rather than volumetric; not standardized across centres; primarily measures regional rather than whole-body composition

PRACTICE

CT-derived skeletal muscle index (L3 SMI) has become a key prognostic marker in oncology, critical illness, and surgical planning. Low L3 SMI identifies patients at high risk of post-operative complications, chemotherapy toxicity, prolonged ICU stay, and reduced survival. Dietitians working in oncology or critical care should understand how to access and interpret CT-derived muscle measurements already available in patient imaging archives — many patients have had CT scans for disease staging that can be repurposed for body composition assessment without additional radiation.

PART THREE — Adiposity: Fat Mass, Fat Location and Metabolic Risk

Not all fat is equal in its metabolic consequences. The location of fat deposits — not just the total amount — is the primary determinant of obesity-related metabolic risk. This section explains why two people with the same total fat mass can have dramatically different cardiometabolic risk profiles.

Adipose Tissue Biology

Visceral Fat, Subcutaneous Fat & Ectopic Fat Deposits

Fat Depot	Location	Metabolic Activity	Cardiovascular & Metabolic Risk
Visceral Adipose Tissue (VAT)	Intra-abdominal: omental, mesenteric, perinephric, and pericardial fat; drains directly into portal circulation	Highly metabolically active; large, insulin-resistant adipocytes; high lipolysis rate; high inflammatory cytokine secretion (TNF- α , IL-6, MCP-1); low adiponectin production	Directly linked to insulin resistance, T2DM, dyslipidaemia (high TG, low HDL), hypertension, and CVD. Portal delivery of free fatty acids and inflammatory mediators to the liver causes NAFLD and promotes systemic insulin resistance. VAT is the primary mechanistic explanation for the 'metabolically obese' phenotype.
Subcutaneous Adipose Tissue (SAT)	Under the skin: abdominal SAT and peripheral SAT (thighs, buttocks, arms)	Lower metabolic activity than VAT; anti-inflammatory properties relative to VAT; higher adiponectin secretion; acts as a metabolic buffer storing lipids away from vital organs	Abdominal SAT contributes to waist circumference measurement. Peripheral SAT (gluteofemoral, 'pear-shaped') is actually inversely associated with metabolic risk in several studies — it acts as a protective buffer that sequesters lipids away from visceral organs.
Intrahepatic Fat (liver steatosis)	Fat stored within hepatocytes	Directly impairs hepatic insulin signaling; promotes hepatic glucose output; the hallmark of NAFLD/NASH	Even modest intrahepatic fat (>5% by weight) is associated with insulin resistance independent of total adiposity. Best measured by MRI (MRI-PDFF) or ultrasound; estimated by waist circumference + metabolic syndrome criteria clinically.
Intramuscular Fat (IMAT)	Fat deposits within skeletal muscle (intermuscular and intramyocellular)	Impairs muscle lipid oxidation; associated with insulin resistance at the cellular level; reflects muscle quality dysfunction, not just muscle quantity	Increased by inactivity, ageing, and obesity. The combination of low muscle quantity + high intramuscular fat = 'myosteatosis' — a severe phenotype associated with poor outcomes in cancer, transplantation, and critical illness. Identified by CT (low HU values in muscle) or MRI.

Pericardial / Epicardial Fat	Fat surrounding the heart and within the pericardial sac	Secretes inflammatory cytokines directly adjacent to coronary arteries	Independently associated with coronary artery disease and arrhythmias; measured by echocardiography or cardiac CT.
Ectopic pancreatic fat	Fat within the pancreas	Impairs β -cell function	Associated with T2DM development; weight loss reduces pancreatic fat and can restore β -cell function in early T2DM (DiRECT trial evidence).

WHY?

This explains the 'metabolically healthy obese' and 'metabolically obese normal weight' (MONW) phenotypes. Metabolically healthy obese individuals have excess total fat mass but relatively low VAT and ectopic fat accumulation — their fat is predominantly subcutaneous peripheral fat. Their metabolic profile can be normal despite high BMI. Conversely, MONW individuals have normal BMI but high VAT and ectopic fat, with normal or low skeletal muscle mass — they have high metabolic risk despite 'normal' weight. BMI cannot distinguish these groups; waist circumference, body composition assessment, and metabolic screening (glucose, lipids, blood pressure) are required.

Adipokines: Fat Tissue as an Endocrine Organ

Adipose tissue is not simply a passive energy store. It is a major endocrine organ that secretes dozens of bioactive proteins (adipokines) with local and systemic effects on metabolism, inflammation, appetite, and cardiovascular function.

Adipokine	Primary Source	Primary Actions	In Obesity/Excess VAT
Adiponectin	Adipocytes (primarily subcutaneous > visceral)	Anti-inflammatory; insulin sensitizer (activates AMPK in liver and muscle); cardioprotective; anti-atherogenic; promotes fatty acid oxidation	Levels inversely proportional to VAT; obese and T2DM patients have low adiponectin — this contributes directly to insulin resistance. Weight loss and exercise increase adiponectin.
Leptin	Adipocytes (proportional to fat mass)	Signals satiety to the hypothalamus (reduces food intake, increases energy expenditure); promotes fatty acid oxidation in peripheral tissues	In obesity: hyperleptinemia + leptin resistance (receptor signaling impaired); analogous to insulin resistance. Hypothalamus fails to respond to leptin's satiety signal. Key mechanism of obesity-driven hyperphagia.

Resistin	Adipocytes and macrophages (primarily in VAT)	Promotes insulin resistance (inhibits insulin receptor signaling in liver)	Elevated in obesity; directly worsens hepatic insulin resistance; links obesity to T2DM via inflammatory mechanism.
TNF- α and IL-6 (pro-inflammatory)	Adipocytes and macrophages in VAT	Promote systemic inflammation; impair insulin receptor signaling (serine phosphorylation of IRS-1); stimulate hepatic acute-phase protein synthesis	Markedly elevated with VAT accumulation; directly cause insulin resistance; elevate hsCRP; contribute to CVD risk. Macrophage infiltration of VAT is a key pathological feature of metabolic obesity.
PAI-1 (plasminogen activator inhibitor-1)	Adipocytes and hepatocytes	Inhibits fibrinolysis (clot breakdown)	Elevated in central obesity; contributes to prothrombotic state; partly explains the increased cardiovascular event risk with obesity.
Visfatin (NAMPT/PBEF)	Visceral adipocytes	Multiple metabolic effects including insulin-mimetic properties; involved in NAD ⁺ synthesis	Research interest as a VAT-specific adipokine; potential biomarker of visceral adiposity.

PART FOUR — Sarcopenia: The Loss of Muscle Mass and Function

Sarcopenia is the progressive, generalized loss of skeletal muscle mass, strength, and function associated with ageing and disease. It is now Recognized as a major clinical syndrome with its own ICD-10 code (M62.84) and is one of the most important drivers of frailty, disability, hospitalization, and mortality in older adults. For the clinical dietitian, sarcopenia represents both an assessment challenge and a primary nutritional intervention target.

Sarcopenia

Definition, Mechanisms, Assessment Criteria & Nutritional Management

Defining Sarcopenia: The EWGSOP2 Framework

The European Working Group on Sarcopenia in Older People (EWGSOP2, 2019) defines sarcopenia as a muscle disease (muscle failure) rooted in low muscle quantity and quality. The diagnostic framework uses three components that must be assessed in sequence:

Component	What It Measures	Primary Assessment Tool	Threshold for Diagnosis
Low Muscle Strength (Probable sarcopenia if this alone is abnormal)	Grip strength — the simplest and most validated measure of overall muscle function and predictor of adverse outcomes	Hand-held dynamometer: maximum isometric grip strength of dominant hand	Low if: <27 kg men / <16 kg women (EWGSOP2). Grip strength predicts hospitalization, falls, disability, and mortality independently of muscle mass.
Low Muscle Quantity or Quality (Confirms sarcopenia when combined with low strength)	Skeletal muscle mass at appendicular level (arms + legs)	DEXA — Appendicular Lean Mass Index (ALMI) BIA — Skeletal Muscle Mass Index (SMI) CT — L3 cross-sectional muscle area	Low ALMI: <7.0 kg/m ² men / <5.5 kg/m ² women (DEXA) Low SMI: <7.0 kg/m ² men / <5.7 kg/m ² women (BIA)
Low Physical Performance (Severe sarcopenia if present with above two)	Functional capacity beyond strength: gait speed, chair stand, balance	Gait speed (4-metre walk test); Short Physical Performance Battery (SPPB); Timed-Up-and-Go test (TUG)	Low gait speed: <0.8 m/s Low SPPB: ≤8/12 Slow TUG: >20 seconds

Mechanisms of Sarcopenia — Why Muscle Is Lost

Mechanism	Biological Pathway	Modifiable by Nutrition?
Anabolic resistance to protein stimulation	Blunted muscle protein synthesis (MPS) response to amino acids (especially leucine) and insulin in aged muscle; reduced mTORC1 activation; impaired satellite cell activation	YES — higher protein doses per meal (30-40g vs 20g) can partially overcome anabolic resistance; leucine-enriched protein (whey, HMB) most effective; spacing protein across meals matters
Hormonal decline	Reduced growth hormone, IGF-1, testosterone, oestrogen with ageing → reduced anabolic signaling; increased cortisol:testosterone ratio in chronic illness promotes catabolism	PARTIAL — resistance exercise restores some hormonal anabolic responsiveness; vitamin D sufficiency supports IGF-1 and muscle function
Chronic low-grade inflammation ('inflammaging')	Elevated IL-6, TNF- α , CRP — particularly from visceral fat and senescent cells — activate NF- κ B in muscle → upregulate ubiquitin-proteasome degradation of muscle proteins	YES — anti-inflammatory dietary patterns (Mediterranean, omega-3 supplementation) reduce IL-6 and TNF- α ; antioxidant-rich foods reduce oxidative stress-driven muscle damage
Physical inactivity and disuse atrophy	Muscle protein synthesis falls dramatically with immobility (as rapidly as 1-2% per day of absolute bed rest); sarcopenia accelerates acutely during hospitalization	YES — early mobilization and resistance exercise are the most effective interventions; even low-intensity resistance exercise preserves muscle during illness

Mitochondrial dysfunction	Reduced mitochondrial biogenesis, impaired oxidative phosphorylation, accumulation of mitochondrial DNA mutations → reduced muscle energy availability and endurance	PARTIAL — exercise (HIIT, endurance) restores mitochondrial function; CoQ10 and PQQ have limited evidence; caloric restriction with adequate protein may slow mitochondrial ageing
Neuromuscular junction denervation	Progressive loss of motor neurons with ageing → denervation of type II fast-twitch muscle fibers; re-innervation by type I fibers → shift from fast to slow muscle fibre type	LIMITED by nutrition alone — resistance exercise stimulates motor neuron health; adequate protein prevents denervation-accelerated atrophy
Inadequate dietary protein intake	Below RDA intake in many older adults; protein distribution skewed to evening meal; inadequate leucine threshold reached at each meal	YES — the most directly actionable nutritional cause; target ≥ 1.2 g protein/kg/day with even distribution across meals; consider BCAA/leucine supplementation

EVIDENCE

PROT-AGE and ESPEN consensus: Adults >65 years should consume ≥ 1.0 -1.2 g protein/kg/day (vs 0.8 g/kg RDA for younger adults) to maintain muscle mass; 1.2-1.5 g/kg/day for those with acute or chronic illness; up to 2.0 g/kg/day for severely malnourished older patients. Protein distribution matters: 30-40g high-quality protein per meal reaches the leucine threshold required to stimulate mTORC1 and maximize MPS. Distributing protein intake across 3 meals is more effective than concentrating it in one large meal. Morning and midday protein intake is often inadequate in older adults — breakfast is a key intervention target.

Sarcopenic Obesity — The Dangerous Combination

Sarcopenic obesity is the co-occurrence of excess adiposity (especially visceral fat) and low skeletal muscle mass. It is the most metabolically dangerous body composition phenotype and is increasingly prevalent as populations age and obesity rates rise simultaneously.

- Prevalence: estimated 10-30% of obese adults over 60 years in high-income countries; rising with the obesity epidemic across all regions.
- Mechanisms: obesity promotes muscle loss through inflammatory adipokines (TNF- α , IL-6) that activate muscle protein degradation; intramuscular fat impairs contractile function; insulin resistance driven by visceral fat blunts anabolic muscle protein synthesis responses.
- Why it is dangerous: the combination of elevated CVD risk (from excess fat) and functional impairment, falls, and disability (from low muscle mass) results in the worst outcomes of any body composition phenotype. The 'obesity protective effect' (where obesity is associated with better survival in some ICU and surgical studies) is largely attributable to patients with high fat but preserved muscle mass — not sarcopenic obese patients.
- Assessment: requires simultaneous measurement of muscle (DEXA, BIA, grip strength) and fat mass (BMI, waist circumference, DEXA). BMI alone systematically misidentifies sarcopenic obesity.
- Treatment: weight loss alone can worsen sarcopenia by reducing muscle mass (all weight loss diets cause some muscle loss without resistance exercise). The combination of moderate caloric restriction + high-protein diet (1.2-1.5 g/kg/day) + resistance exercise is required to lose fat while preserving or building muscle.

PART FIVE — BMI: Uses, Limitations, and When to Look Further

Body Mass Index is the most widely used body composition measure in clinical practice and public health globally — and also the most criticized. Understanding both its legitimate uses and its systematic limitations is essential for any clinical nutritionist.

BMI Category (WHO)	Range	Legitimate Clinical Uses	Known Limitations and When It Fails
Underweight	<18.5	Population-level screening for undernutrition; entry criterion for malnutrition risk tools (MUST, NRS-2002); mortality risk is elevated; trigger for nutritional assessment	Misses oedematous malnutrition (kwashiorkor): patient may have normal BMI due to fluid retention despite severe protein depletion. Does not capture muscle mass loss (sarcopenia) in elderly patients with preserved fat mass.
Normal	18.5–24.9	Low cardiovascular and metabolic risk in most population groups; reference category for epidemiological comparisons	Misidentifies sarcopenic obese normal-weight individuals (high fat, low muscle at normal BMI). Does not account for ethnic variation in risk (Asian adults have higher metabolic risk at BMI 23-25 than White adults).
Overweight	25.0–29.9	Associated with modestly elevated metabolic risk in population studies; trigger for lifestyle counselling	Many muscular individuals with very low fat mass fall in this category (the 'obese athlete' misclassification). Does not distinguish fat from muscle.
Obese Class I	30.0–34.9	Associated with significantly elevated T2DM, CVD, and certain cancer risks at the population level; trigger for clinical assessment and intervention	Large variation in risk within category: 'metabolically healthy obese' vs. high VAT obese have very different risk profiles that BMI cannot distinguish. Waist circumference + metabolic screening essential.
Obese Class II	35.0–39.9	High risk of metabolic complications; bariatric surgery eligibility criterion (BMI ≥ 35 with comorbidity)	Still cannot distinguish fat distribution or muscle mass. A patient with BMI 37 and high muscle mass (powerlifter) may have lower metabolic risk than BMI 30 with high VAT.
Obese Class III	<40.0	Very high risk; bariatric surgery criterion (BMI ≥ 40); associated with substantially reduced life expectancy	At extreme obesity, BIA and skinfold methods are most inaccurate; DEXA is limited by equipment weight capacity; clinical assessment must rely on multiple measures.

CONNECT

Ethnic-specific BMI cut-offs: WHO has acknowledged that the standard BMI cut-offs were derived primarily from European populations. For Asian populations (including populations in Sudan's urban areas who may share metabolic risk profiles with South Asian populations), risk begins at lower BMI thresholds: overweight ≥ 23 kg/m², obese ≥ 27.5 kg/m². Some evidence suggests African-origin populations have different fat distribution patterns and may have different metabolic risk profiles at equivalent BMI to European populations — though this varies considerably by sub-population. The practical message: always supplement BMI with waist circumference and metabolic screening across all ethnic groups.

PART SIX — Special Populations and Clinical Contexts

Body Composition in Malnutrition

Malnutrition involves loss of body cell mass — primarily skeletal muscle and visceral proteins — along with loss of fat mass in starvation, and potentially with preserved or elevated fat mass in inflammatory/disease-related malnutrition (sarcopenic malnutrition). The GLIM criteria (Global Leadership Initiative on Malnutrition, 2018) include low muscle mass as a phenotypic criterion for malnutrition diagnosis alongside low BMI and unintentional weight loss.

Malnutrition Type	Body Composition Profile	Key Assessment Approach	Nutritional Priority
Starvation malnutrition (simple) e.g., anorexia nervosa, food insecurity	Low fat mass; preserved lean mass initially; muscle loss accelerates with prolonged starvation; low BMI	BMI; skinfolds; MUAC; waist circumference; DEXA if available	Gradual refeeding with adequate protein (monitor for refeeding syndrome); increase energy and protein simultaneously; preserve muscle with early mobilization
Disease-related inflammatory malnutrition e.g., cancer, sepsis, CKD, HIV	Muscle mass depleted despite possible normal or elevated fat mass (especially VAT); low grip strength; elevated inflammatory markers (CRP, IL-6)	Grip strength; MUAC; BIA (phase angle as prognostic marker); DEXA ALMI; CT L3 SMI in cancer patients	High protein (1.5-2.0 g/kg/day); anti-inflammatory diet; resistance exercise if possible; address underlying inflammation
Oedematous malnutrition (kwashiorkor in children, anasarca in adults)	Hypoalbuminaemia causes oedema that masks fat and muscle loss; BMI and weight may appear normal or elevated; MUAC may be misleadingly normal if arm is oedematous	MUAC with awareness of oedema artefact; clinical signs of muscle wasting under oedema; serum albumin and pre-albumin (though these are also acute-phase reactants)	Protein-energy repletion; careful diuresis when nutritional status improving; milk-based F-75 and F-100 therapeutic feeds in SAM with kwashiorkor

Body Composition in Athletes

Athletic populations require specialized body composition interpretation because standard reference ranges and BMI cut-offs are derived from sedentary populations. Athletes often have elevated lean mass and low fat mass that places them in 'overweight' or even 'obese' BMI categories.

- Relative Energy Deficiency in Sport (RED-S): Low energy availability (EA) — dietary energy intake minus exercise energy expenditure — below 30 kcal/kg FFM/day causes hormonal suppression (low oestrogen/testosterone), bone loss, immune impairment, cardiovascular dysfunction, and muscle loss regardless of whether body weight is maintained. Body composition assessment (DEXA for bone density, BIA for FFM trends) is central to RED-S monitoring.
- Fat mass minimums: At extreme leanness (<5% fat in men, <12% in women), physiological function is compromised. Essential fat in cell membranes, the CNS, and reproductive organs cannot be eliminated without severe consequences. Athletes pursuing extremely low body fat for aesthetic or weight-class sports face serious health risks.
- Hydration confounding: Athletes' BIA results are highly unreliable due to extreme variation in hydration status (sweat losses, rapid rehydration, glycogen manipulation). DEXA is preferred for athlete body composition assessment.
- Sport-specific body composition: Different sports require different optimal compositions. Endurance athletes: low fat mass maximizes power-to-weight ratio. Strength athletes: high FFM with moderate fat mass. Martial arts and weight-class sports: risk of severe restriction and dehydration to make weight — a health and performance concern.

Body Composition in Older Adults

Ageing produces characteristic shifts in body composition independent of changes in body weight: skeletal muscle mass falls by approximately 3-8% per decade after age 30, accelerating after age 60; fat mass often increases; visceral fat accumulates disproportionately; bone mineral density decreases. Standard BMI cut-offs systematically underestimate metabolic risk in older adults because the 'overweight' weight may include sarcopenic muscle loss with fat gain.

Age-Related Change	Mechanism	Clinical Consequence	Nutritional Intervention
Loss of type II fast-twitch muscle fibers	Motor neuron denervation; reduced anabolic hormone production; disuse; anabolic resistance	Reduced power and speed; increased fall and fracture risk; slowed recovery from illness	Higher protein intake (1.2-1.5 g/kg/day); leucine-enriched protein; resistance exercise; adequate vitamin D
Increased visceral fat	Declining sex hormones (especially oestrogen in women, testosterone in men); reduced physical activity; muscle insulin resistance	Increased T2DM, CVD, and NAFLD risk despite unchanged body weight	Reduce processed carbohydrate and saturated fat; increase dietary fibre and omega-3; resistance +

	increases lipid redistribution to visceral depot		aerobic exercise combination
Decreased bone mineral density	Declining oestrogen (accelerates post-menopause); declining testosterone; reduced calcium absorption; reduced vitamin D status; reduced mechanical loading	Osteoporosis and fragility fractures	Calcium 1200 mg/day; vitamin D 800-1000 IU/day; weight-bearing exercise; avoid smoking and excess alcohol
Decreased total body water	Loss of lean mass reduces intracellular water; impaired thirst mechanism in elderly	Increased dehydration risk; electrolyte disturbances; worsens BIA accuracy (underestimates FFM)	Encourage regular fluid intake on schedule (not relying on thirst); monitor urine colour; increase fluid in hot weather

Clinical Scenario: Integrated Case: Three Patients, One Weight

- Three women present at your outpatient clinic. All are 55 years old, 167 cm tall, and weigh 78 kg (BMI 28.0 — 'overweight'). Their clinical presentations, however, are very different:
- Patient A: Sedentary administrator. Waist circumference 94 cm. Fasting glucose 6.8 mmol/L. TG 2.8 mmol/L, HDL 0.9 mmol/L. Grip strength 14 kg (left hand). Fatigue, no regular exercise.
- Patient B: Former competitive cyclist, now recreational. Waist circumference 72 cm. Grip strength 28 kg. Normal fasting glucose and lipids. Exercises 5 days/week.
- Patient C: Post-menopausal, 6 months post-bilateral knee replacement. Waist circumference 88 cm. Grip strength 12 kg. Has lost 8 kg unintentionally over the past 6 months. Serum albumin 28 g/L. CRP 42 mg/L.
- Question 1: For each patient, use the available clinical data to estimate their likely body composition profile (fat mass, muscle mass, fat distribution). What additional body composition assessment would you request for each, and why?
- Question 2: Patient A's BMI is 28 ('overweight'). Patient B's BMI is also 28. What is the fundamental difference in their body composition and metabolic risk? What does this tell us about the limitations of BMI as a clinical tool?
- Question 3: Apply the EWGSOP2 diagnostic framework to Patient C. What stage of sarcopenia does she likely represent? What are the probable mechanisms of her muscle loss in the context of her recent history and blood results?
- Question 4: Design a nutritional intervention plan for each patient. How do the body composition goals differ for each? What are the specific protein, energy, and micronutrient priorities?
- Question 5: At the 6-month follow-up, you want to assess whether your interventions have changed body composition (not just weight). Which assessment method would you use for each patient, and what specific outcome metrics would you track?

Critical Thinking Questions

- BMI is widely criticised for its limitations, yet it remains the dominant clinical and public health measure of body weight status globally. Given the better alternatives (waist circumference, BIA, DEXA), why does BMI persist? What are the institutional, economic, and practical barriers to replacing or supplementing it — and what would a more accurate, accessible population-level body composition screening system look like?
- Sarcopenia has an ICD-10 code and is Recognized as a disease, yet it is massively underdiagnosed in clinical practice. A hospitalized older patient with low grip strength, muscle wasting, and poor functional capacity may leave hospital without a sarcopenia diagnosis or targeted nutritional management plan. What systemic changes in clinical nutrition practice would be needed to ensure sarcopenia is routinely identified and treated?
- The lecture describes 'sarcopenic obesity' as the most metabolically dangerous body composition phenotype. A patient with this phenotype who is placed on a standard weight-loss diet may actually worsen their sarcopenia while losing fat — achieving the desired weight-loss outcome while worsening their clinical trajectory. How does this challenge the way we typically counsel obese patients, and what does a safe, evidence-based body composition intervention look like for this specific phenotype?

Lecture Summary — Key Takeaways for Dietetic Practice

- Body composition models: 2-compartment (fat mass vs fat-free mass — most field methods), 3-compartment (adds bone mineral), 4-compartment (adds total body water — gold standard research method). Every method embeds assumptions about FFM density and hydration; violations cause systematic errors. Fat-free mass = muscle + bone + water + organs; it determines BMR and functional capacity.
- Assessment methods: Anthropometry (BMI — accessible but limited; waist circumference — better metabolic risk predictor; MUAC — primary field tool for malnutrition in resource-limited settings; skinfolds — technique-dependent). BIA (affordable, accessible, hydration-sensitive; phase angle is a validated prognostic marker). DEXA (best clinical reference; regional analysis; ALMI for sarcopenia diagnosis). CT/MRI (gold standard for VAT and L3 muscle area; CT repurposed from clinical scans in oncology/critical care). Ultrasound (portable, bedside, good for muscle thickness).
- Adiposity and fat location: VAT (visceral adipose tissue) is the primary driver of metabolic risk through inflammatory adipokines (TNF- α , IL-6, resistin), portal free fatty acid delivery, and insulin resistance. Subcutaneous peripheral fat (gluteofemoral) is relatively protective. Ectopic fat (liver, muscle, pancreas) causes organ-specific dysfunction. Adiponectin (anti-inflammatory, insulin-sensitizing) is reduced in obesity; leptin resistance drives hyperphagia. Waist circumference and waist-to-height ratio (0.5 threshold) outperform BMI for metabolic risk prediction.
- Sarcopenia (EWGSOP2 criteria): Low muscle strength (grip <27/16 kg) + low muscle mass (ALMI <7.0/5.5 kg/m²) + low physical performance (gait speed <0.8 m/s). Mechanisms: anabolic resistance, hormonal decline, inflammation, inactivity, mitochondrial dysfunction, denervation. Nutritional

intervention: ≥ 1.2 g protein/kg/day (1.5-2.0 in disease); 30-40g high-quality protein per meal; leucine-enriched sources; even protein distribution. Combined with resistance exercise for maximum effect.

- Sarcopenic obesity: excess fat + low muscle mass = worst metabolic and functional outcomes. Standard weight-loss diets worsen sarcopenia. Requires: high-protein diet (1.2-1.5 g/kg/day) + resistance exercise + moderate caloric restriction. BMI systematically fails to identify this phenotype.

- BMI limitations: does not distinguish fat from muscle; does not capture fat distribution; misclassifies athletes, sarcopenic obese, and many ethnic minorities. Ethnic-specific cut-offs: Asian populations: overweight ≥ 23 , obese ≥ 27.5 . Always supplement BMI with waist circumference + metabolic screening. GLIM criteria use low muscle mass as a diagnostic criterion for malnutrition alongside BMI and weight loss.

Suggested reading:

1. Cruz-Jentoft AJ et al. (2019). Sarcopenia: revised European consensus on definition and diagnosis (EWGSOP2). Age & Ageing. |
2. Jensen MD et al. (2014). AHA/ACC Guideline on Obesity. Circulation. |
3. Wells JCK & Fewtrell MS (2006). Measuring body composition. Archives of Disease in Childhood. |
4. Cederholm T et al. (2019). GLIM criteria for the diagnosis of malnutrition. Clinical Nutrition. |
5. Prado CM et al. (2012). Body composition as an independent determinant of 5-year mortality in patients with colon cancer. Journal of Clinical Oncology. |
6. Baumgartner RN et al. (1998). Epidemiology of sarcopenia among the elderly in New Mexico. American Journal of Epidemiology.

Module 3 — Nutritional Assessment & Specialized Needs

Evaluating Intake & Requirements Across Populations

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Energy Balance & Metabolism

Energy Expenditure, Macronutrient Metabolism, Hunger Regulation & Clinical Energy Prescription

- ▶ Part 1: Total Energy Expenditure — BMR, TEF, AEE & NEAT
- ▶ Part 2: Macronutrient Metabolism — Substrate Hierarchy, RQ & the Fuel Hierarchy
- ▶ Part 3: Hunger, Satiety & Neuroendocrine Regulation — Leptin, Ghrelin, GLP-1, PYY, CCK
- ▶ Part 4: Adaptive Thermogenesis & Metabolic Adaptation — Why Weight Loss Slows
- ▶ Part 5: Clinical Energy Prescription — Critical Illness | Obesity | Cachexia | Pregnancy
- ▶ Clinical Case: Khalid — Office-Based Weight Gain, Plateau & Substrate Metabolism

Energy Balance & Metabolism

Energy Expenditure, Macronutrient Metabolism, Hunger Regulation, Adaptive Thermogenesis & Clinical Energy Prescription

Focus: Why calories are not equal — how the body produces, regulates, and defends energy balance at every level

Why Energy Balance? The Clinical Foundation

Energy balance is the most fundamental principle in clinical nutrition: the relationship between energy intake (from food) and energy expenditure (through metabolism, activity, and thermogenesis) determines body weight, body composition, and metabolic health over time. Yet despite its apparent simplicity — energy in versus energy out — energy balance is one of the most biologically complex and clinically misapplied concepts in all of medicine.

WHY?

The 'calories in, calories out' model is not wrong — it is incomplete. The body is not a passive calorie counter; it is an active regulatory system that continuously adjusts energy expenditure, hunger, substrate oxidation, and hormone secretion in response to changes in intake and body composition. Understanding this regulation is the key to answering the questions that matter clinically: Why does weight loss slow down despite continued caloric restriction? Why do some patients gain weight despite apparently adequate intake? Why does illness raise energy requirements? Why can two patients of the same weight and activity level have very different energy needs? This lecture builds the mechanistic foundation to answer all of these questions.

Learning Outcomes — By the end of this lecture, students will be able to:

- Define and quantify the three components of total energy expenditure (TEE): basal metabolic rate, thermic effect of food, and activity energy expenditure
- Explain the determinants of BMR and apply validated predictive equations (Harris-Benedict, Mifflin-St Jeor, Schofield) with their appropriate clinical contexts
- Describe the metabolic pathways of carbohydrate, fat, and protein as energy substrates — and explain why the body's choice of substrate matters clinically
- Explain the neuroendocrine regulation of hunger, satiety, and energy homeostasis: leptin, ghrelin, GLP-1, PYY, CCK, insulin and hypothalamic integration
- Define adaptive thermogenesis and metabolic adaptation and explain their clinical implications for weight management and nutritional rehabilitation
- Apply energy estimation methods to clinical prescription — including critical illness, obesity, malnutrition recovery, and pregnancy/lactation
- Connect energy balance physiology to the clinical problems of obesity, cachexia, and anorexia nervosa

PART ONE — Total Energy Expenditure: The Three Components

Total Energy Expenditure (TEE) is the total amount of energy the body uses in a defined time period, usually expressed as kcal/day. It is composed of three distinct components that operate through different mechanisms and are influenced by different factors.

The TEE Equation

$$TEE = BMR + TEF + AEE \text{ (+ Thermoregulation in some contexts)}$$

Component	Full Name	% of TEE (sedentary adult)	% of TEE (active adult)	Primary Determinants
BMR	Basal Metabolic Rate — energy expended at complete rest, post-absorptive, thermoneutral environment, 12–14h after last meal	60–70%	45–60%	Fat-free mass (primary), fat mass, age, sex, thyroid hormone, sympathetic nervous system activity, organ mass
REE	Resting Energy Expenditure — measured at rest but not under strict BMR conditions (most clinical measurements)	~same as BMR (+10%)	~same as BMR	Same as BMR; REE is ~10% higher than true BMR because it includes post-absorptive thermogenesis and mild postural muscle tone
TEF	Thermic Effect of Food (Diet-Induced Thermogenesis) — energy used for digestion, absorption, transport, and storage of nutrients	8–10%	5–8%	Macronutrient composition: protein (20–30% of energy); carbohydrate (5–10%); fat (0–3%). Meal size and frequency. Processing degree.
AEE	Activity Energy Expenditure — all energy used above resting in physical movement (both exercise and non-exercise)	20–30%	35–55%	Exercise training; NEAT (Non-Exercise Activity Thermogenesis — fidgeting, posture, spontaneous movement); occupational physical demand
NEAT	Non-Exercise Activity Thermogenesis — component	5–15% of TEE	Variable — major	The most variable component of TEE; varies

	of AEE from all movement except intentional exercise		contributor to inter-individual variation	by up to 2,000 kcal/day between sedentary and active individuals; explains much of why some people gain weight more easily than others
Thermoregulation	Energy used to maintain core body temperature in cold environments or fever	Minor in temperate climates	Minor in temperate climates	Ambient temperature; fever increases REE ~10–13% per °C above 37°C; cold exposure activates brown adipose tissue (BAT) thermogenesis

WHY?

NEAT is the most under-appreciated component of energy balance in clinical nutrition. Research by Levine et al. demonstrated that NEAT accounts for most of the 10-fold difference in AEE between sedentary and highly active individuals. When people gain weight, NEAT tends to decrease (fewer spontaneous movements); when they lose weight, NEAT increases — this is one mechanism by which the body defends its weight set point. Patients who report 'not exercising' may still have very different TEE based on their occupational activity, household tasks, and spontaneous movement. Always ask about both structured exercise and overall daily movement patterns.

Basal Metabolic Rate — The Engine at Rest

BMR represents the minimum energy required to sustain life — maintaining organ function, ionic gradients, protein turnover, thermoregulation, and cellular processes at complete rest. Understanding what drives BMR is essential for accurate energy estimation.

BMR Determinant	Direction of Effect	Magnitude	Clinical Significance
Fat-Free Mass (FFM)	Strong positive: more FFM = higher BMR	~21–22 kcal/kg FFM/day	The primary determinant of BMR. Explains why men have higher BMR than women of the same weight (men have more FFM); why athletes have higher BMR; why sarcopenic patients have low BMR. Muscle is the most metabolically active tissue per kg.
Fat Mass (FM)	Weak positive: more FM = slightly higher BMR	~4.5 kcal/kg FM/day	Fat tissue is metabolically active but far less so than muscle. A 10 kg difference in fat mass adds only ~45 kcal/day to BMR — much less than the same difference in muscle mass (~200 kcal/day).
Age	Negative after ~25 years: BMR falls with age	~1–2% per decade after 25	Largely explained by loss of FFM (sarcopenia) with age. When BMR is expressed per kg FFM, age effects are much smaller. In practice: an older patient's lower BMR is mainly because

			they have less muscle, not because their cells are inherently less active.
Sex	Men higher than women of same weight	~5–10% higher in men	Primarily due to higher FFM in men. When corrected for body composition, sex differences in BMR largely disappear.
Thyroid hormones (T3, T4)	Major positive effect: thyroid hormones regulate mitochondrial uncoupling and cellular metabolic rate	Hyperthyroidism can raise BMR 30–60%; hypothyroidism can lower it 20–40%	The most clinically significant hormonal determinant of BMR. Always consider thyroid status in patients with unexplained weight change. TSH is the primary screening test.
Sympathetic nervous system (SNS)	Positive: catecholamines (adrenaline, noradrenaline) increase BMR	Stress, trauma, surgery, burns can raise BMR 10–80% above baseline	Explains the hypermetabolism of critical illness. ICU patients have markedly elevated REE from sustained SNS activation, cytokine-driven thermogenesis, and wound repair costs. Standard equations systematically underestimate energy needs in sepsis and major burns.
Fever	Positive: each 1°C above 37°C raises BMR ~10–13%	Patient with 40°C fever may have REE 30–40% above baseline	Critical in tropical and resource-limited settings where infectious fever is common. A malnourished child with malaria and high fever has dramatically elevated energy needs at the time when intake is most impaired.
Nutritional status	Complex: starvation and underfeeding lower BMR; overfeeding raises it	Prolonged underfeeding can reduce BMR by 20–30% below predicted	Metabolic adaptation to underfeeding (see Part Five). Key to understanding refeeding energy targets and why BMR-based equations overestimate needs in severely malnourished patients starting nutritional rehabilitation.
Organ composition	Organs (liver, kidney, brain, heart) are highly metabolically active per gram	Brain alone accounts for ~20% of BMR (only 2% of body weight)	This explains why critically ill patients with organ dysfunction have altered energy needs; liver failure, in particular, substantially reduces hepatic metabolic contribution to REE.

Predictive Equations for Energy Estimation

Because direct calorimetry (the gold standard) is impractical in clinical settings, predictive equations estimate BMR or REE from easily measured variables. Accuracy varies between equations and populations. No equation is universally applicable.

Equation	Formula	Validated In	Accuracy	Best Use
Harris-Benedict (1919, revised 1984)	Men: $88.4 + (13.4 \times \text{Wt}) + (4.8 \times \text{Ht}) - (5.7 \times \text{Age})$ Women: $447.6 + (9.2 \times \text{Wt}) + (3.1 \times \text{Ht}) - (4.3 \times \text{Age})$ [Wt = kg; Ht = cm; Age = years]	Healthy North American/European adults; limited ethnic diversity	Overestimates REE in obese patients by 5–15%; underestimates in critically ill; widely used historically	Established adult outpatients; acceptable when more accurate equations unavailable; avoid in extreme obesity or critical illness
Mifflin-St Jeor (1990)	Men: $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{Age}) + 5$ Women: $(10 \times \text{Wt}) + (6.25 \times \text{Ht}) - (5 \times \text{Age}) - 161$ [Wt = kg; Ht = cm; Age = years]	Healthy adults; better than Harris-Benedict in most studies	Most accurate predictive equation for healthy adults; errors $\pm 10\%$ in most individuals; recommended by AND AACE over Harris-Benedict	First choice for healthy and overweight adults; outpatient clinical nutrition practice; weight management programs
Schofield (1985)	Age- and sex-specific equations based on weight alone (and some versions weight + height). Used in WHO technical reports.	Large international dataset including some non-Western populations	Similar accuracy to Harris-Benedict; may be more appropriate for some non-Western populations	Paediatric energy estimation (specific paediatric versions); used in WHO/FAO energy requirement reports; community nutrition programs
Ireton-Jones (1992, revised 2002)	Ventilated: $1784 - (11 \times \text{Age}) + (5 \times \text{Wt}) + (244 \text{ if male}) + (239 \text{ if trauma}) + (804 \text{ if burns})$ Spontaneously breathing: $629 - (11 \times \text{Age}) + (25 \times \text{Wt}) - (609 \text{ if obese})$	ICU patients (ventilated and spontaneously breathing)	Developed for critically ill; moderate accuracy in ICU setting	ICU patients, particularly ventilated; trauma and burns patients
Penn State (2003, 2010)	$\text{Mifflin} \times 0.96 + (\text{T}^{\text{dax}} \times 167) + (\text{Ve} \times 31) - 62$ [T^{dax} = maximum]	Ventilated ICU patients including obese	Best validated equation for critically ill and	Mechanically ventilated ICU patients,

	temperature °C in past 24h; Ve = minute ventilation L/min]		obese ICU patients; consistently outperforms other equations in this population	particularly obese (≥ 30 kg/m ²) or pyrexial patients
Simple weight-based (clinical shortcut)	General: 25–30 kcal/kg/day Critical illness: 20–25 kcal/kg/day (early acute phase) Malnutrition recovery: 30–35+ kcal/kg/day	Broad clinical practice; pragmatic estimates	Less accurate than predictive equations; useful for rapid estimation or when precise measurement unavailable	Bedside rapid estimation; resource-limited settings; initial prescription when sophisticated tools unavailable

CAUTION *Using actual vs adjusted vs ideal body weight in equations: In underweight patients, use actual body weight. In normal weight patients, use actual body weight. In overweight/obese patients: using actual body weight overestimates needs; using ideal body weight (IBW) underestimates needs; use adjusted body weight $[IBW + 0.25 \times (\text{actual BW} - IBW)]$ for patients with BMI >30 in most equations, or apply obese-specific equations (Penn State). In critically ill obese patients, hypocaloric high-protein feeding (60–70% of estimated energy needs with 2.0–2.5 g protein/kg IBW/day) is recommended by ASPEN/SCCM to promote fat mobilization while preserving lean mass.*

Activity Factors: Converting BMR to TEE

To estimate total daily energy needs, the BMR (or REE) is multiplied by a Physical Activity Level (PAL) factor that reflects the overall level of daily activity:

Activity Level	PAL Factor	Example Population	Clinical Application
Sedentary (little or no exercise)	1.2	Bedbound patient; office worker who does not exercise; elderly in residential care	Use 1.2 for bedbound or immobile patients. Most hospitalized patients are close to 1.2.
Lightly active (light exercise 1–3 days/week)	1.375	Walking to work; light household tasks; outpatients with minimal structured exercise	Most ambulatory outpatients with sedentary occupations.

Moderately active (moderate exercise 3–5 days/week)	1.55	Regular recreational exercise; active occupations (nurse, teacher who stands and walks)	Most working adults with some regular exercise.
Very active (hard exercise 6–7 days/week)	1.725	Athletes in training; manual labourers (construction, agriculture)	Farmers, construction workers, athletes in training season.
Extra active (very hard exercise/physical job)	1.9	Professional athletes; military personnel in active training; very heavy manual work	Elite athletes; soldiers in field training. Rare in clinical patient populations.
ICU / critical illness (no PAL applied)	Stress factor 1.0–1.3 applied differently	Mechanically ventilated patients; post-surgical acute phase	In ICU, activity is minimal but hypermetabolism from illness raises REE. Use predictive equations with stress factors OR indirect calorimetry rather than PAL multiplication.

PRACTICE

For hospitalized patients: use PAL 1.2 for bedbound (most acute inpatients); 1.2–1.3 for patients able to mobilize on the ward; 1.3–1.5 for rehabilitation patients. For outpatients: carefully assess actual daily activity (ask about steps, standing time, leisure, household tasks, occupational demands) rather than defaulting to 'sedentary'. Overestimating activity leads to energy prescription that maintains or increases weight when loss is the goal; underestimating leads to inadequate provision and catabolism.

PART TWO — Macronutrient Metabolism: What the Body Burns and Why

The body has three primary macronutrient energy substrates: carbohydrate (glucose, glycogen), fat (fatty acids, triglycerides), and protein (amino acids). It also uses ketone bodies (derived from fat) and, to a very minor degree, alcohol. The choice of which substrate to burn at any moment — the respiratory quotient (RQ) — is not random; it is tightly regulated by substrate availability, hormonal signals, and energy demands.

Substrate Metabolism

Carbohydrate, Fat, Protein & Ketones — The Fuel Hierarchy

Substrate	Energy Yield	Primary Metabolic Pathway	Storage Capacity	RQ (CO ₂ produced / O ₂ consumed)
Glucose (blood)	4 kcal/g	Glycolysis → pyruvate → acetyl-CoA → TCA → ETC (aerobic); Glycolysis → lactate (anaerobic)	~5g (blood); ~80–100g glycogen (liver); ~350–500g glycogen (muscle)	1.0 — equal CO ₂ produced and O ₂ consumed; pure CHO oxidation
Fatty acids (free)	9 kcal/g	β-oxidation of acyl-CoA → acetyl-CoA → TCA → ETC; requires carnitine for mitochondrial entry (long-chain FA)	~12–15 kg in a lean adult (~100,000–130,000 kcal); effectively unlimited	0.71 — fat oxidation produces less CO ₂ per O ₂ consumed; clinically important in ventilated patients
Amino acids (glucogenic/ketogenic)	4 kcal/g	Transamination, deamination → enter TCA at multiple points (pyruvate, oxaloacetate, α-KG, succinyl-CoA, fumarate, acetyl-CoA)	No dedicated protein storage; ~10–11 kg total muscle protein (not all available for energy — functional loss)	~0.82 (mixed; depends on amino acid profile)
Glycerol	4 kcal/g	Released with fatty acid lipolysis; converted to glucose (gluconeogenesis) or enters glycolysis directly	Component of triglyceride structure; quantitatively minor energy source	~1.0 (metabolized similarly to glucose)
Ketone bodies (β-hydroxybutyrate, acetoacetate)	4.7 kcal/g	Synthesized in liver from acetyl-CoA during fat oxidation (fasting, starvation, very low CHO intake, DKA); oxidized in brain, heart, muscle, kidney	Produced on-demand; up to 100–150g/day in prolonged starvation	~0.89
Alcohol (ethanol)	7 kcal/g	Oxidized preferentially in liver (alcohol dehydrogenase → acetaldehyde → acetate); cannot be stored; displaces other substrate oxidation	None — must be oxidized when present	~0.67 — very low RQ

The Respiratory Quotient — A Clinical Window into Substrate Use

The Respiratory Quotient (RQ) = VCO_2 / VO_2 (ratio of CO_2 produced to O_2 consumed). It reflects the mix of substrates being oxidized and has direct clinical relevance for ventilated patients and for indirect calorimetry interpretation.

RQ Value	Interpretation	Clinical Significance
1.0	Pure carbohydrate oxidation	Rarely seen clinically; theoretical maximum for CHO-only diet. An RQ >1.0 indicates de novo lipogenesis (converting glucose to fat) — occurs with extreme carbohydrate overfeeding.
0.85	Mixed substrate oxidation (typical well-fed state)	Normal resting RQ in a person eating a balanced diet. Most indirect calorimetry readings in stable patients fall here.
0.82	Typical Western mixed diet oxidation	Standard assumed value when direct measurement is unavailable.
0.71–0.74	Predominantly fat oxidation	Prolonged fasting, low-carbohydrate diet, ketosis. Expected in malnourished patients and those with very low CHO intake.
>1.0	De novo lipogenesis or hyperventilation	Carbohydrate overfeeding → excess CHO converted to fat, generating more CO_2 than O_2 consumed. Also occurs with hyperventilation (not metabolic). Critical in mechanically ventilated patients: excess CHO feeding raises CO_2 production, increases ventilatory demand, and can make weaning from ventilator impossible.
<0.70	Measurement artefact or unusual substrate mix	Theoretically possible with near-pure alcohol or ketone body oxidation; more often indicates measurement error.

CONNECT

RQ and ventilator weaning: This is one of the most directly clinically actionable applications of substrate metabolism knowledge. In a mechanically ventilated patient who is struggling to wean off the ventilator, high-carbohydrate enteral or parenteral nutrition significantly increases CO_2 production (RQ approaches 1.0 or exceeds it), increasing the work of breathing and making weaning more difficult. Reducing the carbohydrate-to-fat ratio in the nutrition prescription — and avoiding total overfeeding — lowers CO_2 production, reduces minute ventilation requirement, and facilitates weaning. Indirect calorimetry with RQ measurement is the optimal monitoring tool in this situation.

The Fuel Hierarchy: Which Substrate Gets Used When?

The body does not choose substrates randomly. A clear hormonal and metabolic hierarchy governs which fuel is used at any moment, primarily regulated by insulin, glucagon, cortisol, and the sympathetic nervous system:

Metabolic State	Insulin: Glucagon Ratio	Primary Fuels Used	Key Metabolic Events
Fed state (0–2h post-meal)	High insulin, low glucagon	Glucose (primary); some dietary fat absorbed as chylomicrons	Glycogen synthesis (liver and muscle); triglyceride synthesis and storage in adipose; protein synthesis stimulated; hepatic glucose output suppressed; fat oxidation suppressed
Post-absorptive state (4–8h after last meal)	Falling insulin; rising glucagon	Glucose from liver glycogen; beginning of fat mobilization	Liver glycogenolysis maintains blood glucose; insulin-stimulated glucose uptake in muscle falls; adipose lipolysis begins; some increase in fatty acid oxidation
Short-term fasting (8–24h)	Low insulin, higher glucagon	Liver glycogen (depleted after 12–16h); increasing fatty acids; beginning gluconeogenesis	Muscle glycogen used for local needs only; hepatic glycogen depleted; gluconeogenesis accelerates (substrates: alanine, lactate, glycerol); fat oxidation increases significantly; ketogenesis begins
Prolonged fasting (24h–7 days)	Very low insulin; high glucagon; rising cortisol and growth hormone	Fatty acids (primary); ketone bodies (increasing); gluconeogenesis from amino acids (muscle protein breakdown)	Accelerating lipolysis; ketone production rises to spare glucose; brain begins using ketone bodies (reducing protein catabolism); RQ falls toward 0.71; urine ketones detectable
Starvation (>7 days)	Minimal insulin; high glucagon, cortisol, GH	Predominantly fat (fatty acids + ketones); minimal glucose (gluconeogenesis maintained for obligate glucose users: RBCs, renal medulla, parts of CNS)	Ketoadaptation: brain uses 70–75% of energy from ketone bodies, reducing glucose demand to ~80g/day; protein catabolism rate falls to minimum (~30–40g protein/day); survival prolonged by fat reserves
Critical illness / trauma	Variable; often insulin resistance + counter-regulatory hormones dominant	Glucose (despite insulin resistance; forced by cytokines); increasing protein catabolism	Hyperglycaemia despite normal or elevated insulin (insulin resistance); muscle protein breakdown accelerated by cortisol and cytokines; fat mobilization impaired; high REE; different from starvation — protein cannot be spared by ketone adaptation

WHY?

Critical illness is metabolically completely different from starvation — and this distinction fundamentally changes the nutrition approach. In starvation, the body adapts to protect protein by switching to fat/ketone oxidation. In critical illness, the counter-regulatory hormones (cortisol, glucagon, catecholamines) and inflammatory cytokines (IL-6, TNF- α) override this adaptation and drive mandatory glucose oxidation and accelerated muscle protein breakdown that cannot be stopped by providing ketones or fat. This is why critically ill patients lose 1–2% of their skeletal muscle per day of ICU stay regardless of nutritional support — the catabolism is driven by the inflammatory response, not by insufficient substrate provision alone. Nutrition in the acute phase of critical illness cannot prevent catabolism; it can only limit its severity.

Thermic Effect of Food — Why Protein Costs More to Process

Macronutrient	TEF (% of energy ingested)	Mechanism	Clinical Relevance
Protein	20–30%	Deamination of amino acids (excretion of urea nitrogen requires ATP); active transport of amino acids across gut and tissues; peptide bond synthesis; the most metabolically 'expensive' nutrient to process	High-protein diets have a significant thermogenic advantage — a diet providing 1500 kcal with 30% protein has a net available energy ~100–150 kcal lower than one with 10% protein from the same total calories. This partly explains why high-protein diets support weight loss beyond caloric restriction alone.
Carbohydrate	5–10%	Active transport and phosphorylation; glycogen synthesis (requires ATP); moderate cost relative to protein	Moderate thermogenic effect; processing complex carbohydrates (with fibre) costs slightly more energy than simple sugars due to fermentation and slower digestion
Fat	0–3%	Fatty acids are readily incorporated into chylomicrons with minimal processing costs; very similar structure to stored triglycerides — low conversion cost	Very low thermogenic effect — dietary fat is metabolically 'cheap' to process and store. This does not mean fat is more 'fattening' per calorie than CHO; the energy density (9 kcal/g vs 4 kcal/g) is the more important practical consideration.
Mixed meal (balanced diet)	8–10% overall	Weighted average of macronutrient TEF contributions	The standard 10% TEF correction applied to BMR in clinical practice is a reasonable approximation for most diets
Ultra-processed foods	Estimated 30–40% lower TEF than whole foods providing equivalent macronutrients	Mechanical and industrial pre-processing reduces the digestive work required; soft, uniform texture lowers chewing and gastric processing costs	A diet of ultra-processed foods provides more net energy per calorie than an equivalent diet of minimally processed whole foods — a biological explanation for the higher obesity risk associated with ultra-processed food consumption independent of caloric content.

PART THREE — Hunger, Satiety & the Neuroendocrine Regulation of Energy Balance

Food intake is not simply a matter of willpower or conscious choice. It is governed by a complex neuroendocrine system that integrates signals from the gut, adipose tissue, pancreas, and brainstem with higher cognitive, emotional, and hedonic inputs. Understanding this system explains why hunger and satiety cannot be overridden by instruction alone — and why biological factors, not character flaws, drive excessive food intake in many patients.

The Hunger-Satiety System

Hypothalamic Integration of Peripheral Signals

The Hypothalamus: Central Integration Hub

The arcuate nucleus (ARC) of the hypothalamus is the primary central processor of energy balance signals. It contains two populations of opposing neurons that together regulate appetite and metabolic rate:

Neuron Population	Neuropeptides Released	Effect on Energy Balance	Activated By
Orexigenic neurons (hunger-promoting)	NPY (Neuropeptide Y) — most potent orexigen; AgRP (Agouti-Related Peptide) — also blocks melanocortin receptors	Increase food intake; decrease energy expenditure; stimulate fat storage; decrease thermogenesis	Fasting; low leptin; high ghrelin; hypoglycaemia; elevated cortisol; weight loss (adaptive response)
Anorexigenic neurons (satiety-promoting)	POMC (Pro-opiomelanocortin) — cleaved to α -MSH; CART (Cocaine and Amphetamine-Regulated Transcript)	Decrease food intake; increase energy expenditure; promote fat oxidation; increase thermogenesis	Feeding; high leptin; low ghrelin; elevated GLP-1 and PYY; elevated glucose and insulin; weight gain

The ARC neurons project to other hypothalamic nuclei (PVN, LH, VMH, DMH) and to the brainstem NTS (nucleus tractus solitarius), which integrates gut-derived vagal signals. The result is coordinated regulation of meal initiation, meal termination, and long-term energy homeostasis.

The Major Appetite-Regulating Hormones

Hormone	Source	Primary Signal	Effect on Appetite	Effect on Metabolism	Clinical Relevance
Leptin	Adipocytes (proportional to fat mass)	Long-term energy stores (chronic signal)	Suppresses appetite (activates POMC/CART; inhibits NPY/AgRP)	Increases energy expenditure; stimulates fat oxidation; permissive for reproduction and thyroid function	In obesity: leptin resistance (receptor signaling impaired despite high levels) — the satiety signal is present but cannot be heard. Weight loss improves leptin sensitivity. Low leptin in anorexia nervosa and extreme leanness causes persistent hunger and metabolic suppression.
Ghrelin	Gastric fundus cells (X/A-like cells)	Short-term pre-meal hunger signal	Potent appetite stimulant (activates NPY/AgRP neurons)	Decreases energy expenditure; promotes fat storage; stimulates GH release	The only known peripheral hormone that increases appetite. Rises before meals, falls after. Also elevated by: caloric restriction (explains why dieting makes you hungrier), poor sleep, chronic stress. Suppressed by: food intake, bariatric surgery (Roux-en-Y gastric bypass dramatically reduces ghrelin — partly explains its superior weight loss vs restrictive procedures).
GLP-1 (Glucagon-Like Peptide-1)	L-cells of distal small intestine and colon	Post-meal nutrient detection	Suppresses appetite (acts on hypothalamus and brainstem); delays gastric emptying (slows absorption)	Potent insulin secretagogue; suppresses glucagon; improves insulin sensitivity	Basis of GLP-1 receptor agonist medications (semaglutide, liraglutide, dulaglutide) — the most effective anti-obesity pharmacotherapy currently available. Also released by bariatric surgery. Stimulated by: protein and fat reaching the distal gut; dietary

					fibre fermentation products (SCFAs).
PYY (Peptide YY)	L-cells (co-released with GLP-1)	Post-meal satiety signal	Suppresses appetite (inhibits NPY/AgRP in ARC)	Minor metabolic effects	Co-secreted with GLP-1; contributes to post-meal satiety. Attenuated in obesity (contributes to reduced satiety response after meals). High-fibre and high-protein diets increase PYY secretion, contributing to their satiety-enhancing effects.
CCK (Cholecystokinin)	I-cells of proximal small intestine	Fat and protein in duodenum	Short-term meal termination signal; acts on vagal afferents and brainstem	Stimulates pancreatic enzyme and bile secretion; slows gastric emptying	Short-acting meal termination signal. Released when fat and protein reach the duodenum — explains why low-fat, low-protein meals (white rice, refined carbohydrates) are less satiating per calorie than mixed meals.
Insulin	Pancreatic β -cells	Blood glucose and amino acids (post-meal)	Suppresses appetite in CNS (long-term signal proportional to insulin resistance and fat mass)	Primary anabolic hormone: stimulates glucose uptake, glycogen synthesis, lipogenesis, protein synthesis; suppresses lipolysis	In insulin resistance and obesity: impaired insulin CNS signaling contributes to reduced satiety. Hyperinsulinaemia in T2DM drives fat storage and weight gain. Meal composition affects post-prandial insulin response: high GI foods cause rapid insulin spikes followed by hypoglycaemia-driven rebound hunger.
Cortisol	Adrenal cortex (stress-activated)	Stress, sleep deprivation, caloric restriction	Increases appetite (particularly for energy-dense, palatable foods — stress eating); activates	Promotes muscle protein catabolism; stimulates hepatic gluconeogenesis; promotes visceral fat deposition;	Chronic psychological stress, poor sleep (<7 hours), and caloric restriction all raise cortisol. This is a key mechanism linking stress and sleep deprivation to obesity and difficulty with

			NPY/AgRP pathway	inhibits insulin sensitivity	weight management. Cortisol-driven preference for ultra-processed, energy-dense foods has evolutionary origins (stress → energy mobilization) but is maladaptive in chronic form.
Adiponectin	Adipocytes (inversely proportional to fat mass)	Long-term metabolic health signal	Modest appetite effects; primarily metabolic	Insulin-sensitizing (activates AMPK); anti-inflammatory; promotes fat oxidation; cardioprotective	Reduced in obesity; increased by weight loss, exercise, and Mediterranean diet. Low adiponectin is a biomarker of metabolic dysfunction independent of BMI.

EVIDENCE

GLP-1 receptor agonists and energy balance: Semaglutide (Ozempic/Wegovy) at 2.4 mg/week produced 15% body weight loss in the STEP-1 trial (n=1961, 68-week RCT) vs 2.4% placebo — the largest pharmacological weight loss effect demonstrated in an RCT at the time of publication. The mechanism: GLP-1 RA suppresses hypothalamic NPY/AgRP neurons, reduces reward-driven eating in the nucleus accumbens, slows gastric emptying, and reduces postprandial glucose excursions. Weight regain after stopping is rapid and nearly complete, confirming that obesity is a chronic neuroendocrine disease requiring ongoing treatment — not a reversible behaviour problem.

The Gut-Brain Axis: Vagal Signaling and Gut Microbiome Effects

The gut communicates appetite and satiety information to the brain through multiple channels: hormonal (as above); neural (vagal afferents carrying mechanosensory and chemosensory signals from the gut wall to the NTS); and microbial (gut bacteria produce short-chain fatty acids, indoles, and other metabolites that directly activate enteroendocrine cells and modulate appetite hormone secretion).

- Vagal stretch receptors in the stomach wall signal meal volume (gastric distension) to the NTS — this is a volume-based satiety signal independent of caloric content. Explains why high-water, high-fibre, low-energy-density foods (vegetables, fruits, soup) produce satiety at lower energy intake.
- Vagal chemoreceptors detect fat and protein in the small intestine and signal via CCK to the brainstem to terminate eating — a quality-of-food satiety signal.
- Gut microbiome → SCFAs (acetate, propionate, butyrate) from dietary fibre fermentation → stimulate GLP-1 and PYY secretion from colonic L-cells → satiety. This is one mechanism by which high-fibre diets reduce energy intake beyond their direct effect on gastric distension.

- Microbiome composition affects energy harvest from food: some Firmicutes-dominant microbiomes extract more energy from the same food than Bacteroidetes-dominant microbiomes — a biological contributor to inter-individual variation in weight gain from identical diets.

PART FOUR — Adaptive Thermogenesis and Metabolic Adaptation

The human body does not passively accept changes in energy intake. When energy intake falls below expenditure — whether through dieting, illness-related anorexia, or starvation — the body activates a coordinated metabolic adaptation response that reduces energy expenditure below what body composition alone would predict. This is adaptive thermogenesis: one of the most powerful and most clinically relevant metabolic phenomena in human physiology.

Metabolic Adaptation

The Body's Defense of Body Weight Against Caloric Restriction

What Is Metabolic Adaptation?

Metabolic adaptation (also called adaptive thermogenesis) is the reduction in energy expenditure that occurs beyond what is expected from changes in body weight and body composition alone during periods of energy restriction. In other words: when you eat less, your body not only uses less energy because you have less mass — it also uses less energy per unit of mass. This component is metabolic adaptation.

Component of Energy Adaptation	Mechanism	Magnitude	Reversibility
Reduced REE due to weight/muscle loss	Less metabolically active tissue = less energy needed; each kg of FFM lost reduces REE by ~21 kcal/day	~200–400 kcal/day for 10 kg weight loss	Reverses fully with weight regain if body composition is restored
True metabolic adaptation (beyond composition changes)	Reduced sympathetic nervous system activity; reduced thyroid hormone (T3) production; increased mitochondrial efficiency (less heat wasted per ATP produced); reduced NEAT; reduced reproductive and immune hormonal activity	~100–500 kcal/day (varies enormously between individuals; in The Biggest Loser study, mean metabolic adaptation was ~700 kcal/day at 6	Partially persists long after weight loss; may not fully reverse even with weight restoration; contributes to weight regain

		years post-competition)	
Reduced TEF	Smaller meals + reduced metabolic rate = less thermogenic cost of eating	~50–100 kcal/day reduction in TEF	Reverses with restoration of normal eating
Reduced NEAT (fidgeting, spontaneous movement)	CNS-mediated reduction in spontaneous movement; less energy wasted in subconscious activity	~100–200 kcal/day; large inter-individual variation	Partially reverses; NEAT suppression is a major but under-Recognized contribution to weight loss plateau
Increased muscle efficiency	Muscles require less oxygen per unit of work after weight loss (improved mechanical efficiency)	~10–15% increase in efficiency; ~150–200 kcal/day impact in active individuals	Partially reverses over time

EVIDENCE

The Biggest Loser study (Fothergill et al., 2016, Obesity): 14 participants from the extreme weight loss TV competition (average 58 kg weight lost) were followed 6 years post-competition. Despite regaining most of their lost weight, metabolic adaptation persisted: REE remained ~700 kcal/day below predicted for their body composition at 6 years. The more weight regained, the greater the metabolic adaptation persisted. This study provided the most compelling human evidence that metabolic adaptation is a long-lasting biological response to major weight loss — not simply a transient diet effect.

Clinical Implications of Metabolic Adaptation

Metabolic adaptation has several critically important clinical implications that every dietitian must understand:

- **Weight loss plateau:** After initial weight loss, metabolic adaptation reduces TEE — meaning the same caloric deficit that caused weight loss initially will eventually become maintenance, then insufficient for further loss. This is biological, not a failure of willpower or adherence. Counselling patients about this prevents them from concluding that 'the diet has stopped working' when in reality they need to either further reduce intake or increase activity.
- **Weight regain after diet:** Metabolic adaptation persists after weight loss ends, reducing energy needs below the pre-diet level. If intake returns to pre-diet levels, there is a positive energy balance and weight regain — often exceeding the original weight. This is the metabolic mechanism behind yo-yo dieting and the high long-term weight regain rate seen after dietary interventions without sustained behaviour change.
- **The Leibel et al. principle:** Maintaining a reduced body weight requires approximately 500–700 kcal/day less intake than a person who has never been overweight at the same body weight — because of persistent metabolic adaptation.

- Implications for refeeding in malnutrition: Severely malnourished patients have undergone profound metabolic adaptation — their REE may be 20–30% below what standard equations predict for their current body weight. Starting refeeding at full estimated requirements risks overfeeding and refeeding syndrome complications. Always start below calculated requirements and advance gradually.
- Resistance training as a counter-measure: Building or preserving muscle mass during weight loss is the most effective strategy to counter metabolic adaptation. Muscle mass preserves REE; resistance training during weight loss reduces the proportion of weight lost as lean tissue.

CAUTION

Extreme energy restriction and metabolic adaptation: Very low calorie diets (VLCD, <800 kcal/day) produce rapid early weight loss but accelerate metabolic adaptation significantly, preserve less lean mass, and result in more severe and persistent post-diet metabolic suppression than moderate restriction (~500–750 kcal/day deficit). Except in specific medically supervised contexts (preparation for bariatric surgery; severe obesity with immediate health risk), VLCDs are generally not recommended as long-term weight management strategies because of the rebound weight regain driven by metabolic adaptation.

Brown Adipose Tissue (BAT) and Non-Shivering Thermogenesis

Brown adipose tissue is a specialized fat depot with high mitochondrial density (giving it its brown colour) that generates heat through uncoupled oxidative phosphorylation. Uncoupling Protein 1 (UCP1) allows protons to bypass ATP synthase, dissipating the proton gradient as heat rather than ATP. BAT is activated by cold exposure and sympathetic stimulation.

- BAT in humans: Present in significant amounts in newborns (thermogenesis without shivering); previously thought absent in adults; 18F-FDG PET studies demonstrated metabolically active BAT in adult humans in the supraclavicular, neck, and paravertebral regions. Quantity declines with age and obesity.
- Clinical relevance: BAT activation by cold exposure can increase energy expenditure by 100–300 kcal/day. Research interest in pharmacological BAT activation (beta-3 adrenergic agonists, bile acids) as an obesity treatment target. Currently no established clinical interventions, but cold exposure protocols are being studied.
- Beige/brite adipocytes: White adipose tissue can be induced to express UCP1 and acquire BAT-like thermogenic properties ('browning') by cold exposure, exercise (irisin from muscle), and certain dietary compounds (capsaicin, curcumin, resveratrol — modest effects). A potential future target for metabolic therapy.

PART FIVE — Energy Balance in Clinical Conditions

The physiology of energy balance is transformed in the context of specific clinical conditions. Understanding these disease-specific alterations is essential for appropriate energy prescription.

Clinical Energy Estimation

Critical Illness, Obesity, Malnutrition, Cachexia & Special Populations

Critical Illness: Hypermetabolism and the Phases of Response

Critical illness produces a stereotyped metabolic response that evolves in phases. Nutrition prescription must be adapted to each phase — providing too much energy in the early acute phase may be as harmful as providing too little in the anabolic phase.

Phase	Timeline	Metabolic State	Energy Target	Rationale
Early acute (Ebb phase)	0–24h after insult	Hypometabolism: reduced cardiac output, hypothermia, shock, severely impaired substrate utilization	Minimal or no nutrition; IV glucose for glucose-dependent tissues only (100–200 kcal/day of dextrose)	Cells cannot use nutrients effectively during haemodynamic instability; early aggressive feeding increases risk of complications (hyperglycaemia, CO ₂ load, gut ischaemia, immunosuppression from insulin surges)
Late acute (Flow phase)	24–120h (days 1–5)	Hypermetabolism: elevated REE 20–80% above baseline; insulin resistance; mandatory glucose oxidation; accelerated muscle protein catabolism despite nutrition	Hypocaloric: 70–80% of measured or estimated energy needs; protein 1.2–1.5 g/kg IBW/day for non-obese; higher protein for obese (2.0–2.5 g/kg IBW)	Autophagy (cellular self-digestion of damaged components) during mild caloric restriction may be beneficial; hyperglycaemia from full feeding increases complications; protein targets prioritized over energy targets in early acute phase
Post-acute (anabolic/recovery)	Day 5 onwards to discharge	Anabolic: transitioning to anabolism; insulin resistance improving; rebuilding lean mass	Full or hypercaloric energy provision: 25–30 kcal/kg/day; protein 1.5–2.0 g/kg/day;	Muscle rebuilding requires adequate energy + protein + physical activity; this phase is often under-treated nutritionally

			progressive mobilization	despite being the period when nutritional rehabilitation has the greatest impact
Rehabilitation	Post-ICU to restoration of function	Variable: may still have significant catabolism, malnutrition, muscle weakness, dysphagia	Individualized: assess body composition; target >25–30 kcal/kg with >1.2–1.5 g protein/kg/day; monitor for POST-ICU syndrome nutritional needs	Post-ICU syndrome (PICS) includes profound muscle wasting, cognitive impairment, and psychological dysfunction that require sustained nutritional and rehabilitative support

Obesity: Estimating Energy Needs for Weight Management

Energy prescription for weight management in obesity requires balancing the need for a sustainable caloric deficit with preservation of lean mass, metabolic health, and long-term adherence. The goal is not maximum weight loss speed but optimal body composition change.

- Caloric deficit for weight loss: 1 kg of adipose tissue $\approx$ 7,700 kcal. A deficit of 500 kcal/day theoretically produces $\approx$ 1 kg/month weight loss. In practice, metabolic adaptation means actual weight loss is 30–40% less than predicted by the simple deficit model. Real-world sustainable targets: 0.5–1.0 kg/week weight loss for most patients; 0.5 kg/week is more realistic and better for lean mass preservation.
- Protein priority: High protein intake (1.2–1.6 g/kg IBW/day) during weight loss preserves lean mass, maintains higher REE, increases satiety (via GLP-1, PYY, CCK), and reduces adaptive thermogenesis compared to lower-protein diets of equal caloric content. This is the single most evidence-supported dietary modification for improving body composition during weight loss.
- Energy prescription approach: Calculate TEE using adjusted body weight or Mifflin-St Jeor; subtract 500–750 kcal/day for 0.5–1.0 kg/week loss target. Minimum: 1200 kcal/day women, 1500 kcal/day men (below these thresholds, micronutrient adequacy and lean mass preservation are compromised without supplementation).
- Dietary pattern evidence: Mediterranean, DASH, and high-protein/low-GI patterns show comparable long-term weight loss (6–12 months) to low-fat or low-carbohydrate diets when total energy is matched. Adherence and dietary preference are the primary determinants of long-term success — no single macronutrient composition is universally superior for weight loss.

Disease-Related Malnutrition and Cachexia

Condition	Energy Characteristic	Metabolism	Energy Target	Key Nutritional Priority
Cancer cachexia	Elevated REE in some tumor types (especially lung, pancreatic, colorectal); impaired lipid oxidation; insulin resistance; anabolic resistance; mandatory glucose oxidation driven by tumor (Warburg effect); inflammation-driven muscle catabolism		25–30 kcal/kg/day; caution against aggressive overfeeding which may feed tumor preferentially in some contexts	High protein (1.5–2.0 g/kg/day); anti-inflammatory dietary pattern; omega-3 fatty acids (EPA 2–3 g/day has evidence for attenuating cachexia); address anorexia pharmacologically if severe; appetite stimulants (megestrol, dexamethasone short-term)
Heart failure	Cardiac cachexia in advanced HF: elevated REE from increased respiratory and cardiac work; malabsorption from gut oedema; anorexia; diuretic-induced K, Mg losses		25–28 kcal/kg/day; fluid restriction 1.5–2L/day depending on severity; sodium restriction 1.5–2g Na/day	Avoid fluid and sodium excess (worsen oedema); monitor K/Mg with diuretics; thiamin supplementation (loop diuretics deplete thiamin); small frequent meals (large meals increase cardiac demand); cardiac rehabilitation nutrition support
COPD	Elevated REE from increased work of breathing; air trapping and hyperinflation raise diaphragm energy cost; nutritional depletion common (30–40% of COPD patients malnourished)		Avoid overfeeding; match energy to measured REE; balance CHO:fat ratio to reduce CO ₂ production (RQ target 0.80–0.85)	Protein 1.2–1.5 g/kg/day; reduce CHO proportion; supplement antioxidants (C, E, selenium); treat concurrent sarcopenia; pulmonary rehabilitation
CKD (pre-dialysis)	REE may be modestly elevated by uraemia and anaemia; protein restriction limits protein as an energy substrate		30–35 kcal/kg/day to prevent protein catabolism with protein restriction	Low-protein diet (0.6–0.8 g/kg/day) with adequate non-protein energy to prevent protein catabolism; plant-dominant protein reduces phosphate and sulphate load; phosphate, potassium restriction; vitamin D supplementation

Anorexia nervosa	Profound metabolic adaptation: REE 20–40% below predicted for current weight; hypothyroidism (low T3 from euthyroid sick syndrome); bradycardia; lowered core temperature; reduction in all energy expenditure components	Start: 800–1200 kcal/day (not more); advance 200 kcal/day every 3–5 days; target final intake 2000–3500+ kcal/day for weight restoration (metabolic adaptation means needs rise significantly as weight restores)	Thiamin BEFORE refeeding (refeeding syndrome risk); phosphate, K, Mg monitoring daily; never normalize calories suddenly; weight restoration target 0.5–1.0 kg/week inpatient; cardiac monitoring during refeeding; address energy avoidance and food fear simultaneously with psychological treatment
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Energy Requirements in Pregnancy and Lactation

Stage	Additional Energy Required	Protein Requirement	Key Micronutrient Priorities
First trimester (0–13 weeks)	No significant additional energy needed above pre-pregnancy TEE in most women (embryo and placenta are tiny)	No change above pre-pregnancy RDA	Folate 400–600 µg/day (neural tube closure occurs weeks 3–4, often before pregnancy confirmed); vitamin D; iron screening
Second trimester (14–26 weeks)	+340 kcal/day above pre-pregnancy TEE	Additional +10–15 g/day above pre-pregnancy RDA (total ~71 g/day for most women)	Iron (requirements double; supplementation usually needed); calcium (1000 mg/day); iodine (+50 µg/day above baseline)
Third trimester (27–40 weeks)	+452 kcal/day above pre-pregnancy TEE; higher requirements reflect foetal fat deposition and maternal preparation for lactation	Same as second trimester	Omega-3 DHA for foetal brain development (200 mg/day; more if no fish intake); vitamin K; continue iron, folate, vitamin D
Lactation (exclusive breastfeeding)	+330–400 kcal/day above pre-pregnancy TEE (human milk = ~70 kcal/100 mL; producing 800–900 mL/day requires ~500 kcal/day of which ~150 kcal comes from fat mobilization)	Additional +19–25 g/day protein for milk protein synthesis	Calcium 1000 mg/day; vitamin D; iodine; choline; continue prenatal supplement; vitamin B12 critical for breastfed infant of vegan mother

CONTEXT

Pregnancy energy requirements in Sudan and East Africa: Malnutrition during pregnancy is both prevalent and high-stakes in Sudan. Low maternal BMI at conception, inadequate gestational weight gain, and micronutrient deficiencies (iron, folate, iodine, zinc) independently increase risks of preterm birth, low birth weight, neural tube defects, and maternal mortality. In populations where maternal malnutrition is prevalent, additional energy supplementation above the standard trimesters targets may be needed. The UNHCR/WFP BSFP (Blanket Supplementary Feeding Program) for pregnant and lactating women provides supplementary food rations specifically to address this need in crisis settings.

Clinical Scenario: Integrated Case: Khalid, 44 years old, Khartoum

- Khalid is a 44-year-old male civil engineer presenting for a nutrition consultation. He is 178 cm tall and weighs 97 kg (BMI 30.6). He reports gaining 18 kg over the past 3 years since changing jobs from a site-based role (daily physical activity) to an office-based management position. He works 10–12 hours daily sitting at a desk. He eats lunch and dinner only (skips breakfast), usually fast food at lunch and a large home-cooked dinner. He sleeps 5–6 hours per night due to work stress. He has no medical diagnoses. Fasting glucose 5.9 mmol/L; TG 2.6 mmol/L; HDL 0.88 mmol/L; waist circumference 104 cm.
- Question 1: Using the Mifflin-St Jeor equation, calculate Khalid's estimated BMR. Apply an appropriate PAL factor to estimate TEE. What total energy intake would create a 500 kcal/day deficit for a target weight loss of approximately 0.5 kg/week?
- Question 2: Identify all the physiological mechanisms contributing to Khalid's weight gain over the past 3 years beyond the obvious reduction in physical activity. Consider specifically: NEAT, sleep deprivation effects on appetite hormones, meal timing and meal skipping, and the substrate use implications of his dietary pattern.
- Question 3: Khalid asks why his weight loss has slowed after 6 weeks despite 'sticking to 1800 kcal/day.' Explain the biological mechanisms of metabolic adaptation that account for this plateau — without using the phrase 'you need to try harder.'
- Question 4: Design the macronutrient composition of Khalid's 1800 kcal diet, specifying protein, carbohydrate, and fat targets in grams and percentages. Justify each target with reference to the energy balance and appetite regulation physiology covered in this lecture.
- Question 5: Khalid is sceptical that 'all calories are equal' — he read online that 100 kcal from protein, carbohydrate, and fat are 'completely different.' Construct a scientifically accurate response that explains both what is true and what is misleading in this claim, drawing on TEF, substrate oxidation, RQ, appetite hormone responses, and gut hormone effects.

Critical Thinking Questions

- The lecture describes obesity as a chronic neuroendocrine disease driven by leptin resistance, ghrelin dysregulation, impaired GLP-1/PYY satiety signaling, and persistent metabolic adaptation following weight loss — all of which make sustained weight loss biologically difficult for most people. Yet obesity is still widely stigmatised as a failure of willpower or self-discipline. How should this mechanistic

understanding change the language, tone, and framing of clinical nutrition counselling for patients with obesity? What specific language shifts would you make?

- Adaptive thermogenesis means that a severely malnourished patient (e.g., with anorexia nervosa or SAM) has a profoundly lower REE than standard equations predict. Starting nutritional rehabilitation at 'full calculated requirements' risks refeeding syndrome; starting too low risks inadequate recovery. How would you design a step-wise refeeding protocol for a patient with anorexia nervosa and BMI 14 using the energy physiology from this lecture? What monitoring parameters would you specify?

- The RQ principle in mechanical ventilation suggests that reducing carbohydrate and increasing fat in the nutrition prescription reduces CO₂ production and facilitates weaning. However, some clinicians argue that the total energy load matters more than macronutrient composition for CO₂ production. Synthesize the evidence: is it total energy, macronutrient composition, or both that drive CO₂ burden in mechanically ventilated patients? What practical nutrition prescription guidance follows from this?

Lecture Summary — Key Takeaways for Dietetic Practice

- Total Energy Expenditure: TEE = BMR (60–70%) + TEF (8–10%) + AEE (20–30%). BMR is primarily determined by fat-free mass (~21–22 kcal/kg FFM). NEAT (spontaneous movement) is the most variable component — varies 500–2000 kcal/day between individuals. Predictive equations: Mifflin-St Jeor (best for healthy adults); Penn State (best for mechanically ventilated/obese ICU patients); weight-based (25–30 kcal/kg) for rapid bedside estimation.

- Macronutrient metabolism: Glucose (RQ 1.0); fat (RQ 0.71); protein (RQ ~0.82); mixed diet (RQ 0.82–0.85). RQ >1.0 = lipogenesis (excess CHO overfeeding) — critical in ventilated patients (raises CO₂, impairs weaning). TEF: protein 20–30% > carbohydrate 5–10% > fat 0–3%. Fuel hierarchy: glucose preferred in fed state → glycogen → fat + gluconeogenesis in fasting → ketone adaptation in prolonged starvation. Critical illness breaks this hierarchy: mandatory glucose oxidation + accelerated muscle catabolism that nutrition cannot fully prevent.

- Neuroendocrine regulation: Arcuate nucleus balances orexigenic (NPY/AgRP) vs anorexigenic (POMC/CART) neurons. Key hormones: Leptin (adipose — long-term satiety signal; resistant in obesity); Ghrelin (stomach — only peripheral orexigen; rises with caloric restriction); GLP-1 (distal gut — satiety + insulin secretion; basis of semaglutide); PYY (co-released with GLP-1); CCK (proximal gut — meal termination via fat/protein detection); Insulin (CNS satiety; impaired in insulin resistance). Sleep deprivation and chronic stress raise cortisol + ghrelin and reduce leptin — a direct biological pathway from stress and poor sleep to weight gain.

- Adaptive thermogenesis: Metabolic adaptation reduces TEE beyond what weight loss alone predicts by 100–700 kcal/day through reduced SNS activity, lower T₃, increased mitochondrial efficiency, reduced NEAT, and muscle efficiency gains. Persists long after weight loss (The Biggest Loser study: ~700 kcal/day suppression at 6 years). Clinical implications: explains weight loss plateau, yo-yo dieting biology, and why malnourished patients need careful graduated refeeding (their REE is 20–30% below predicted). Counter-measure: resistance training to preserve lean mass during weight loss.

- Clinical energy prescription: Critical illness (early acute: 70–80% of estimated needs; protein priority; late/recovery: 25–30 kcal/kg + 1.5–2.0 g protein/kg). Obesity (500–750 kcal/day deficit; high protein

1.2–1.6 g/kg IBW; Mediterranean/high-protein pattern). Cancer cachexia (25–30 kcal/kg; EPA 2–3 g/day; address anorexia). Pregnancy (+340 kcal/day T2; +452 kcal/day T3; folate before conception; DHA 200 mg/day; iron + iodine supplementation). Anorexia nervosa (start 800–1200 kcal/day; advance slowly; thiamin before refeeding; electrolyte monitoring daily).

Suggested reading:

1. Hall KD et al. (2012). Quantification of the effect of energy imbalance on body weight. Lancet. |
2. Levine JA (2004). Non-exercise activity thermogenesis. Proc Nutr Soc. |
3. Fothergill E et al. (2016). Persistent metabolic adaptation 6 years after 'The Biggest Loser' competition. Obesity. |
4. Wilding JPH et al. (2021). Once-Weekly Semaglutide in Adults with Overweight or Obesity (STEP-1). NEJM.
5. Singer P et al. (2019). ESPEN guidelines on clinical nutrition in the intensive care unit. Clinical Nutrition. |
6. Morton GJ et al. (2006). Central nervous system control of food intake and body weight. Nature.

Module 3 — Nutritional Assessment & Specialized Needs

Evaluating Intake & Requirements Across Populations

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Nutritional Assessment

From Screening to Diagnosis — Tools, Biomarkers, Dietary Methods & the ADIME Framework

- ▶ Part 1: Screening vs. Assessment — Two Different Questions
- ▶ Part 2: Validated Screening Tools — MUST | NRS-2002 | MNA | STAMP | PG-SGA
- ▶ Part 3: The ABCDE Assessment Framework — Anthropometric | Biochemical | Clinical | Dietary | Environmental
- ▶ Part 4: Diagnosing Malnutrition — The GLIM Criteria
- ▶ Part 5: The Nutrition Care Process — ADIME Documentation & the PES Statement
- ▶ Part 6: Population-Level Assessment — SMART Surveys, GAM, SAM & Sudan Context
- ▶ Clinical Case: Hana — Elderly Malnutrition, Social Isolation & ADIME Documentation

Nutritional Assessment

From Screening to Diagnosis — Tools, Biomarkers, Dietary Methods & the ADIME Framework

Focus: Why we assess, what we measure, how we interpret — and how to turn data into a clinical nutrition diagnosis

Why Nutritional Assessment? The Clinical Case

Malnutrition — in all its forms — is one of the most prevalent yet underdiagnosed conditions in clinical medicine. Hospital malnutrition affects 20–50% of inpatients across all settings. It increases complication rates, prolongs hospital stays, impairs wound healing and immune function, and raises mortality. Yet studies consistently show that malnutrition is identified in fewer than half the patients who have it. The reason is not that clinicians lack access to the patient — it is that they lack a systematic assessment approach.

WHY?

Nutritional assessment is not a single test or a single number. It is a structured clinical reasoning process that integrates multiple data streams — anthropometric, biochemical, clinical, and dietary — to answer four fundamental questions: (1) Does this patient have malnutrition? (2) If so, what type and severity? (3) What is the cause? (4) What nutritional intervention does the evidence support? This lecture builds the framework and tools to answer all four questions rigorously.

Learning Outcomes — By the end of this lecture, students will be able to:

- Distinguish between nutritional screening and nutritional assessment, and explain when each is appropriate
- Apply the major validated screening tools (MUST, NRS-2002, MNA, STAMP) and interpret their scores in clinical context
- Conduct a systematic nutritional assessment using the ABCDE framework (Anthropometric, Biochemical, Clinical, Dietary, Environmental/Social)
- Interpret key biochemical markers of nutritional status, understand their limitations as nutrition indicators, and identify the conditions that confound their interpretation
- Describe the major dietary assessment methods (24-hour recall, food frequency questionnaire, food diary, dietary history, observation) with their strengths, weaknesses, and appropriate uses
- Apply the GLIM criteria for malnutrition diagnosis and the ADIME framework for nutrition care documentation
- Identify the specific assessment challenges and population-level nutrition indicators relevant to Sudan, East Africa, and resource-limited settings

PART ONE — Screening vs. Assessment: Two Different Questions

Nutritional screening and nutritional assessment are often used interchangeably but they serve fundamentally different clinical purposes and require different tools, time, and expertise.

Dimension	Nutritional Screening	Nutritional Assessment
Purpose	Identify patients who are malnourished or AT RISK of malnutrition and require further evaluation	Comprehensively characterize the type, severity, and cause of malnutrition in patients already identified as at-risk
Who performs it	Any trained healthcare worker: nurse, doctor, dietitian, pharmacist	Registered dietitian or clinical nutrition specialist
Time required	2–5 minutes	30–60+ minutes for full assessment
Tools used	Validated brief tools: MUST, NRS-2002, MNA, STAMP, SNAQ	ABCDE framework: anthropometry, biochemistry, clinical examination, dietary intake, environmental/social factors
Output	Risk score: low / medium / high risk	Nutrition diagnosis using GLIM criteria or PES statement; care plan
When to screen	On admission to hospital or residential care; at first outpatient contact; repeat every 1–2 weeks in hospital	After positive screen; before starting nutrition support; for complex nutritional problems
Sensitivity vs specificity	Designed for high sensitivity (catch all at-risk patients, accept some false positives)	Designed for diagnostic accuracy (precise characterization)

PRACTICE

The clinical workflow is: SCREEN first (quick, simple, universal) → if at risk: ASSESS fully (comprehensive, specialist-led) → DIAGNOSE malnutrition (GLIM criteria) → PLAN nutritional care (energy, protein, route, monitoring) → MONITOR and REASSESS. Skipping screening leads to missed malnutrition. Skipping assessment after a positive screen leads to poorly targeted interventions. Both steps are necessary.

PART TWO — Validated Screening Tools

A nutritional screening tool must be: brief, simple to administer, valid (predicts malnutrition-related outcomes), reliable (consistent between raters), and practical for the clinical setting. The following tools are the most widely validated and internationally used.

Malnutrition Universal Screening Tool (MUST)

Community, Primary Care & Hospital Settings — Any Adult

MUST was developed by BAPEN (British Association for Parenteral and Enteral Nutrition) and validated across hospital, community, and primary care settings. It uses three components:

MUST Component	Score 0	Score 1	Score 2
Step 1: BMI (kg/m ²)	>20.0	18.5–20.0	<18.5
Step 2: Unintentional weight loss (past 3–6 months)	<5%	5–10%	>10%
Step 3: Acute disease effect (no nutritional intake likely for >5 days)	N/A (score 0 if no acute disease)	N/A	Score 2 if acutely ill AND no nutritional intake likely for >5 days

Total MUST Score	Risk Category	Recommended Action
0	Low risk	Routine re-screen: monthly (hospital), annually (community)
1	Medium risk	Observe: document dietary intake for 3 days; if adequate — continue monitoring; if inadequate — improve and monitor
2 or above	High risk	Refer to dietitian; initiate nutritional support; set goals; monitor and review

CAUTION

MUST limitations: BMI requires accurate height and weight (often difficult in bedside settings); it does not include a functional or dietary intake component; it does not capture the severity of inflammation that drives disease-related malnutrition. When height cannot be measured (bed-bound, spinal curvature), use ulna length, knee height, or demi-span with validated conversion equations. When weight cannot be measured, use clinical judgement of visible wasting or MUAC.

Nutritional Risk Screening 2002 (NRS-2002)

Hospital Inpatients — Recommended by ESPEN

NRS-2002 was developed by Kondrup et al. and recommended by ESPEN as the first-line hospital screening tool. It adds a disease severity component to capture the catabolic drive of illness — recognizing that a patient with a serious illness has increased nutritional requirements even if their weight is normal.

NRS-2002 Component	Score 0	Score 1 (Mild)	Score 2 (Moderate)	Score 3 (Severe)
Nutritional Status	Normal nutritional status	Wt loss >5% in 3 months OR food intake <50–75% of normal requirement in past week	Wt loss >5% in 2 months OR BMI 18.5–20.5 + impaired general condition OR food intake 25–50% of normal in past week	Wt loss >5% in 1 month (>15% in 3 months) OR BMI <18.5 + impaired general condition OR food intake 0–25% of normal in past week
Disease Severity (catabolic stress)	Normal nutritional requirements	Hip fracture; chronic disease (cirrhosis, COPD, chronic HD, diabetes, cancer)	Major abdominal surgery; stroke; severe pneumonia; hematological malignancy	Head injury; bone marrow transplant; ICU patients (APACHE >10)

Total score = Nutritional Status score + Disease Severity score. If patient is ≥70 years: add 1 point to total.

- Score ≥3: patient is nutritionally at risk — initiate nutritional plan
- Score <3: weekly re-screening; if patient is scheduled for major surgery, consider pre-operative nutritional support

WHY?

The disease severity component is NRS-2002's most important feature. A patient with BMI 22 and no weight loss might score 0 on nutritional status — but if they have just had a bone marrow transplant (score 3 on disease severity), their total score is 3 and they are at high nutritional risk. This is the correct clinical judgment: the transplant patient will have severely impaired intake, massively elevated catabolism, and immunosuppression that makes optimal nutrition critical. NRS-2002 captures this; MUST does not.

Mini Nutritional Assessment (MNA)

Older Adults (≥65 years) — Community, Residential Care & Hospital

The MNA was specifically designed and validated for older adults, who have different nutritional risk profiles from younger hospital patients. It exists in two versions:

MNA Version	Components	Scoring	Action
MNA-Short Form (MNA-SF) 6-item screen	Food intake decline; weight loss; mobility; psychological stress or acute disease; neuropsychological problems; BMI (or calf circumference if BMI unavailable)	0–11: possible malnutrition → proceed to full MNA; 12–14: normal nutritional status — re-screen in 3 months	Screening only; positive screen triggers full MNA
Full MNA 18 items	MNA-SF + additional: lives independently?; medication; pressure sores; meals/day; food groups consumed; fluid intake; mode of feeding; self-perceived nutrition status; self-perceived health vs others; mid-arm circumference; calf circumference	<17: malnourished; 17–23.5: at risk of malnutrition; 24–30: normal nutritional status	Full nutritional assessment and care plan if score <17 or 17–23.5

CONTEXT

The MNA includes calf circumference (<31 cm = reduced muscle mass) as an alternative to BMI — making it useful when weight or height cannot be measured. In community settings in Sudan and resource-limited environments where BMI measurement is impractical, MNA's calf circumference component combined with food intake questions provides a clinically valid rapid screening approach for elderly patients visiting health centres.

Other Validated Screening Tools

Paediatric, Surgical & Specialized Settings

Tool	Full Name	Target Population	Key Features
STAMP	Screening Tool for Assessment of Malnutrition in Paediatrics	Children aged 1–16 in hospital	Three components: diagnosis (does this condition carry nutritional risk?), nutritional intake, weight and height centile. Score ≥ 4 : high risk; 2–3: medium; 0–1: low.
STRONG Kids	Screening Tool for Risk on Nutritional Status and Growth	Children aged 1 month–17 years in hospital	4-item tool: high-risk disease; subjective clinical assessment; nutritional intake and losses; weight loss or low weight for height. Score 4–5: high risk; 1–3: medium; 0: low.
PG-SGA	Patient-Generated Subjective Global Assessment	Cancer patients (adult)	Patient-completed section (weight history, dietary intake, symptoms, activity/function) + clinician-scored section (disease/metabolic demand, physical examination of fat, muscle, fluid). Gold standard for oncology nutrition assessment. Score ≥ 9 : critical need for nutritional intervention.
SNAQ	Short Nutritional Assessment Questionnaire	Hospital adults	4-item tool: unintentional weight loss in past 6 months (≥ 6 kg = 3 points; 1–6 kg = 2 points); reduced appetite last month; use of nutritional supplements or tube feeding. Score ≥ 3 : malnourished; 2: at risk.
MUST (adapted)	Malnutrition Universal Screening Tool	Pregnant women, dialysis patients, critical care	MUST with adjusted reference ranges or supplementary questions. Widely used but requires clinical adaptation for each population.

PART THREE — The ABCDE Assessment Framework

A full nutritional assessment systematically collects data across five domains, each providing different and complementary information about the patient's nutritional status. No single domain is sufficient alone — a patient can have normal biochemistry but severe muscle wasting; another can have low albumin due to inflammation with no actual nutritional depletion. The integration of all five domains enables accurate diagnosis.

A — Anthropometric Assessment

Height, Weight, BMI, Body Composition & Growth Monitoring

Anthropometry provides objective, reproducible measurements of body size and composition. It is the first and most accessible domain of nutritional assessment. The principles, methods, and limitations of anthropometric measurements are covered in depth in the Body Composition lecture; the focus here is on their role within the overall assessment framework.

Measurement	What It Assesses	Key Clinical Interpretation Points
Weight (current and historical)	Total body mass; weight change over time	Unintentional weight loss is one of the most powerful indicators of malnutrition: >5% in 3 months or >10% in 6 months is clinically significant. Always calculate percentage weight loss, not just absolute kg. Oedema masks true weight loss — an oedematous patient may gain scale weight while losing lean tissue.
Height	Reference for weight, BMI, and growth	Measure standing height with stadiometer. If standing is impossible: estimate from ulna length, knee height, or demi-span using validated age- and sex-specific conversion tables. Do not use patient-reported height — adults overestimate height by 1–2 cm on average.
BMI (Weight/Height ²)	Crude adiposity proxy at population level	Limitations detailed in Body Composition lecture. In assessment context: BMI <18.5 is a GLIM phenotypic criterion for malnutrition; BMI >30 does not exclude malnutrition (sarcopenic obesity). Adjust cut-offs for age (elderly: BMI 22–26 as the healthier range) and ethnicity.
Unintentional weight loss (%)	Magnitude of recent nutritional depletion	Formula: (Usual weight – Current weight) / Usual weight × 100. Clinically significant: >5% in 1 month, >7.5% in 3 months, >10% in 6 months. Severe: >10% in 1 month.
MUAC	Rapid proxy for lean mass; primary tool in humanitarian settings	<185 mm: at risk of malnutrition in adults. <125 mm: severe acute malnutrition in children 6–59 months. Serial MUAC is the primary admission/discharge criterion for therapeutic feeding programs in Sudan and the Sahel. Not affected by oedema in the arm.

Calf circumference	Muscle mass proxy in elderly	<31 cm associated with low muscle mass. Useful in elderly patients where BMI is less reliable. Included in MNA.
Skinfold measurements	Subcutaneous fat at specific sites	Operator-dependent; technique must be standardized. Useful for longitudinal monitoring in stable populations. Less reliable in oedema, extreme obesity, or severe wasting.
Growth monitoring (children)	Weight-for-age, height-for-age, weight-for-height (WHO growth standards)	Stunting: height-for-age Z-score <-2 (chronic malnutrition); Wasting: weight-for-height Z-score <-2 (acute malnutrition); Underweight: weight-for-age Z-score <-2. Plot on WHO growth charts at every visit.

B — Biochemical Assessment

Laboratory Markers of Nutritional Status — Interpretation and Limitations

Biochemical markers can objectively quantify specific nutrient levels or functional parameters related to nutrition. However, every biochemical marker of nutritional status is confounded by non-nutritional factors — principally inflammation, hydration status, and organ function. Understanding these confounders is as important as knowing the normal reference ranges.

Marker	What It Measures	Normal Range	Critical Confounders & Interpretation Pitfalls
Serum albumin	Visceral protein pool (hepatic synthesis)	35–50 g/L	Half-life ~21 days: slow to reflect recent changes. MOST IMPORTANT CONFOUNDER: albumin is a negative acute-phase reactant — liver preferentially synthesizes CRP and other acute-phase proteins during inflammation at the expense of albumin synthesis. Low albumin in hospitalized patients primarily reflects acute or chronic inflammation, NOT protein malnutrition. Oedema also lowers albumin by dilution. Cannot be used alone to diagnose protein malnutrition in inflamed or acutely ill patients.
Pre-albumin (Transthyretin)	Visceral protein; thyroid hormone and retinol transport	200–400 mg/L (20–40 mg/dL)	Half-life ~2 days: responds faster than albumin. SAME CONFOUNDER: also a negative acute-phase reactant; falls with inflammation and rises with recovery regardless of nutritional intervention. Falls in CKD due to reduced clearance, in zinc deficiency (zinc required for synthesis), in liver disease, and in hyperthyroidism.
C-Reactive Protein (CRP)	Acute-phase inflammation	<10 mg/L	Used ALONGSIDE albumin/pre-albumin to interpret them. If albumin is low AND CRP is high: inflammation is the cause, not protein depletion

	marker; NOT a direct nutrition marker		alone. If albumin is low AND CRP is normal: more likely to reflect true protein depletion.
Transferrin	Iron transport protein; secondary visceral protein marker	200–360 mg/dL	Half-life ~8–9 days. Also a negative acute-phase reactant; also elevated in iron deficiency (independent of nutritional status). Less specific for nutrition than pre-albumin.
Haemoglobin & haematocrit	Carries oxygen; reflects iron, B12, folate, and protein adequacy	Men: 130–175 g/L; Women: 120–155 g/L	Anaemia is common in malnutrition but has many causes. MCV (mean corpuscular volume): low in iron deficiency or thalassaemia; high in B12/folate deficiency. Always investigate aetiology before attributing anaemia to nutrition.
Serum iron, TIBC, ferritin	Iron stores and transport capacity	Ferritin: 15–300 µg/L (lower limit: <15 = depleted stores)	Ferritin is a positive acute-phase reactant: elevated in inflammation regardless of iron stores. Low ferritin is specific for iron depletion; elevated ferritin does NOT exclude iron deficiency in inflamed patients. Transferrin saturation <16% confirms functional iron deficiency even with elevated ferritin.
Serum 25(OH) vitamin D	Vitamin D status (total — dietary + cutaneous)	Sufficient: >50 nmol/L (>20 ng/mL)	Widely deficient in hospital patients and the general population. In Sudan and sunny climates: deficiency is common despite sun exposure in those with covered skin, those who avoid sun, and the elderly. Serum level affected by season, skin pigmentation, obesity (sequestration in fat).
Serum zinc	Zinc status (insensitive marker)	11–17 µmol/L	Serum zinc is a poor proxy for total body zinc (zinc has no dedicated storage; serum level maintained at expense of tissue levels). Falls with inflammation (zinc redistributes intracellularly as acute-phase response). Low serum zinc is meaningful mainly when consistent with clinical signs and dietary assessment.
Serum retinol (vitamin A)	Vitamin A status	0.7–3.5 µmol/L	Does not reflect liver stores until severely depleted (<0.7 µmol/L). Falls with infection and inflammation. In VAD-endemic areas (Sudan, Sub-Saharan Africa), clinical signs (night blindness, Bitot's spots) + dietary assessment are often more informative than serum retinol alone.
Lymphocyte count (TLC)	Proxy for immune competence related to nutrition	1.5–4.0 × 10 ⁹ /L	TLC <1.5 × 10 ⁹ /L associated with moderate malnutrition; <0.9 severe. Highly non-specific: lymphopenia from many causes. Only useful as one element among many; not a standalone nutrition marker.
Blood glucose (fasting and HbA1c)	Glycaemic status; long-term glucose control	Fasting: 3.9–6.1 mmol/L; HbA1c <5.7% (normal)	Essential in nutrition assessment because hyperglycaemia drives muscle catabolism via insulin resistance; uncontrolled diabetes causes micronutrient losses (Zn, Mg, B1). HbA1c reflects 3-

			month average; unreliable in haemolytic anaemia and haemoglobinopathies.
Serum electrolytes (Na, K, Mg, PO4)	Fluid and electrolyte status	Na 135–145 mEq/L; K 3.5–5.0; Mg 0.7–1.0 mmol/L; PO4 0.8–1.5 mmol/L	Critical before and during nutritional support. Low phosphate + low Mg + low K in a malnourished patient starting feeds = refeeding syndrome risk. Always check before initiating nutritional support.
Nitrogen balance	Protein anabolism vs catabolism	Positive balance = anabolism	N balance = Protein intake (g/day) ÷ 6.25 – (UUN + 4). Requires 24h urine urea nitrogen collection. Used in ICU and research to assess whether protein provision matches catabolic losses. Rarely done in routine clinical practice.

CAUTION

The albumin trap: Albumin is frequently documented in clinical notes as a nutrition marker with statements like 'albumin is 22 g/L, indicating severe protein malnutrition.' In the majority of hospitalized patients, low albumin reflects inflammation-driven redistribution, not protein depletion. Using albumin to diagnose malnutrition in acutely ill patients without interpreting CRP concurrently leads to over-diagnosis of malnutrition, inappropriate enteral nutrition orders, and missed diagnosis of the true problem (inflammation requiring treatment). Always interpret albumin alongside CRP, clinical context, and dietary assessment.

C — Clinical Assessment

Physical Examination, Medical History & Functional Status

Clinical assessment integrates findings from the medical history, physical examination, functional status, and medication review. It is the domain most dependent on clinical reasoning and synthesis — integrating diverse information into a coherent nutritional picture.

Medical and Nutritional History

History Domain	Key Questions	Nutritional Significance
Weight history	Usual weight; maximum and minimum weights; timeline of changes; intentional vs unintentional	Percentage weight loss over defined periods is the most powerful screening criterion. Recent rapid loss more clinically significant than slow gradual loss.
Dietary history (brief)	Appetite; recent food intake changes; food avoidance; nausea, vomiting, dysphagia; recent fasting periods	Reduced oral intake is the most common proximate cause of hospital malnutrition. Duration and magnitude of intake reduction predicts risk.

GI function	Nausea, vomiting, diarrhoea, constipation, bloating; surgical history (especially bowel resections)	Malabsorption from short bowel syndrome, IBD, coeliac disease, pancreatic exocrine insufficiency. Post-gastrectomy: B12, iron, calcium malabsorption.
Medical diagnoses	Chronic diseases; recent acute illness; surgery; infections	Disease-specific nutritional risk: cancer (cachexia), CKD (phosphate, potassium, protein restriction), liver disease (protein, branched-chain AA), HIV/AIDS (wasting, micronutrient deficiency), heart failure (fluid restriction, sodium restriction, cardiac cachexia).
Medications	All current medications including supplements	Drug-nutrient interactions: methotrexate (folate antagonist); isoniazid (B6 antagonist); warfarin (vitamin K interaction); diuretics (K, Mg, Zn wasting); statins (CoQ10 depletion); PPIs (B12, Mg, Ca, iron malabsorption); oral corticosteroids (Ca, K, glucose effects); cholestyramine (fat-soluble vitamin malabsorption).
Social history	Living situation; cooking ability; food access; income; food security; social support	Food insecurity is a major driver of malnutrition that cannot be addressed by diet alone. Identify need for social support, food assistance, or community nutrition programs.
Psychological history	Anxiety, depression, eating disorders	Depression reduces appetite and food motivation. Eating disorders profoundly affect intake patterns and require specialist psychological co-management alongside nutrition support.

Physical Examination for Nutritional Deficiency — Clinical Signs by System

Body System / Site	Clinical Sign	Associated Deficiency
Hair	Alopecia; dull, sparse, easily pluckable hair; flag sign (alternating light and dark bands)	Protein-energy malnutrition; zinc; biotin; selenium. Flag sign: alternating periods of adequate and inadequate nutrition.
Face/Eyes	Pallor of conjunctiva	Iron, B12, folate, copper deficiency anaemias
Face/Eyes	Bitot's spots (foamy white patches on conjunctiva); night blindness; corneal xerosis; keratomalacia	Vitamin A deficiency (VAD). Common in Sudan and Sub-Saharan Africa. Bitot's spots are pathognomonic of VAD.
Face/Eyes	Corneal vascularisation	Riboflavin (B2) deficiency
Face/Mouth	Angular cheilitis (fissures at corners of mouth); stomatitis	B2, B3, B6, iron deficiency
Face/Mouth	Glossitis (red, swollen, smooth tongue)	B2, B3, B6, B12, folate, iron
Face/Mouth	Bleeding, spongy gums	Vitamin C deficiency (scurvy)
Face/Mouth	Dental enamel defects; mottling	Fluoride excess (fluorosis) or deficiency; severe vitamin D deficiency in childhood

Skin	Perifollicular petechiae; follicular hyperkeratosis (rough, dry skin with keratin plugs)	Vitamin C deficiency; vitamin A deficiency
Skin	Photosensitive dermatitis (Casal's necklace, glove and boot distribution)	Niacin deficiency (pellagra)
Skin	Nasolabial seborrhoea; scrotal/vulval dermatitis	B2, B6 deficiency
Skin	Oedema (pitting)	Protein-energy malnutrition (kwashiorkor); thiamin deficiency (wet beriberi); hypoalbuminaemia
Skin	Poor wound healing; perifollicular haemorrhage; 'corkscrew' hairs	Vitamin C deficiency (scurvy)
Skin	Acrodermatitis (perioral, perianal, acral rash)	Zinc deficiency
Musculoskeletal	Muscle wasting (visible loss of muscle bulk, especially temporalis, thenar, hypothenar, interossei, quadriceps)	Protein-energy malnutrition; prolonged inactivity; disease-related cachexia
Musculoskeletal	Bone pain; rachitic rosary; bow legs in children; Looser zones in adults	Vitamin D deficiency (rickets/osteomalacia)
Musculoskeletal	Tetany; Trousseau's sign; Chvostek's sign	Hypocalcaemia (vitamin D deficiency, hypomagnesaemia, hypoparathyroidism)
Neurological	Peripheral neuropathy (sensory loss, paraesthesiae, reduced reflexes)	B1 (thiamin), B12, B6 (megadose toxicity), vitamin E deficiency
Neurological	Confusion, ophthalmoplegia, ataxia	Thiamin deficiency (Wernicke's encephalopathy)
Neurological	Cognitive decline; subacute combined degeneration	B12 deficiency
Nails	Koilonychia (spoon-shaped nails)	Iron deficiency
Nails	Transverse white lines (Muehrcke's lines)	Hypoalbuminaemia
Thyroid	Goitre (diffuse thyroid enlargement)	Iodine deficiency — endemic in many inland African regions

CONTEXT

Clinical signs of nutritional deficiency in Sudan and the wider East Africa/Sahel region: The most clinically important to Recognize are: Bitot's spots and night blindness (VAD — endemic in rural Sudan, particularly in children); goitre (iodine deficiency — especially inland regions far from iodized salt supply chains); oedematous malnutrition with skin changes (kwashiorkor — most prevalent in children 6 months–2 years in food-insecure households); pellagra skin changes (niacin deficiency — seen in sorghum/maize-dominant diets without adequate protein diversity); and signs of acute severe malnutrition (visible severe wasting, MUAC <125 mm in children). The clinical examination must be interpreted in the context of the local food system and epidemiological background.

Functional Assessment

Functional status is an independent predictor of nutritional risk and clinical outcomes, often more sensitive than biochemical markers or anthropometry in identifying clinically significant nutritional depletion.

Functional Assessment Tool	What It Measures	Clinical Utility
Handgrip strength (dynamometry)	Maximum isometric grip force; primary EWGSOP2 criterion for sarcopenia diagnosis	Most validated functional nutrition marker: predicts post-operative complications, hospital length of stay, and mortality independently of BMI or albumin. Low grip strength: <27 kg men / <16 kg women. Sensitive to recent changes in nutritional status (falls with malnutrition, rises with repletion faster than muscle mass). Simple, inexpensive, reproducible.
Short Physical Performance Battery (SPPB)	Three components: balance test, 4-metre gait speed, 5-times chair stand test. Each scored 0–4; total 0–12	Score ≤8: low physical performance; component of severe sarcopenia diagnosis. Predicts hospitalization, disability, and mortality in older adults. Practical in outpatient and rehabilitation settings.
6-Minute Walk Test (6MWT)	Distance walked in 6 minutes at comfortable pace	Validated in respiratory, cardiac, and oncology patients. Reflects cardiorespiratory and functional capacity. Changes >30m are clinically meaningful. Used to monitor response to nutritional and exercise interventions.
Timed-Up-and-Go Test (TUG)	Time to rise from chair, walk 3 metres, return, and sit	>12 seconds: identifies patients at fall risk; >20 seconds: severe physical performance limitation in EWGSOP2. Practical one-item test for rapid clinic assessment.
Activities of Daily Living (ADL) / IADL	Independence in basic (ADL) and instrumental (IADL) activities	Low ADL/IADL scores reflect functional dependency that impairs the ability to prepare, obtain, and consume adequate food — a direct nutritional risk.
Subjective Global Assessment (SGA)	Clinician-rated global nutrition rating (A = well-nourished; B = moderately malnourished; C = severely malnourished) based on history + physical exam	Validated, reproducible, inexpensive. Good inter-rater reliability when trained. Does not produce a numerical score — categorical output. The PG-SGA adapts SGA specifically for cancer patients.

D — Dietary Assessment

Quantifying What Patients Actually Eat

Dietary assessment aims to quantify or characterize an individual's food and nutrient intake for comparison against estimated requirements or dietary reference values. No single method captures intake perfectly — all have sources of error and are appropriate for different purposes.

Method	Principle	Strengths	Limitations	Best Use
24-Hour Dietary Recall	Trained interviewer (or self-report) elicits all food and beverages consumed in the preceding 24 hours using a structured multiple-pass approach	Low respondent burden; no literacy required; suitable for diverse populations; can be conducted by phone; multiple recalls can estimate usual intake (2–5 days recommended)	Single recall reflects one day, not habitual intake (high day-to-day variability); relies entirely on memory; portion size estimation is difficult; interviewer skill affects quality; 'flat slope syndrome' (overweight under-report, underweight over-report)	Individual clinical assessment; population surveys (NHANES, national dietary surveys); monitoring change in intake during nutrition support
Food Frequency Questionnaire (FFQ)	Respondent reports how often they consume items from a structured food list over a defined reference period (usually 1 month or 1 year) with or without portion size information	Captures habitual intake over long periods; low cost; can be self-administered; suitable for large epidemiological studies; validated for specific populations	Low absolute accuracy for nutrient amounts; highly dependent on food list completeness and cultural appropriateness; cognitive burden for long retrospective recall; not suitable for clinical individual assessment in ill patients	Epidemiological research; population-level nutrient intake estimation; diet-disease association studies; assessing habitual dietary patterns rather than precise nutrient intakes
Prospective Food Diary (Weighed or Estimated)	Respondent records all food and drink in real time over 3–7 days; weighed diary requires food scales; estimated diary uses household measures or descriptions	Most accurate method for measuring short-term intake; no memory bias; can capture day-to-day variation; weighed diary is the reference standard for dietary methods	High respondent burden (affects compliance and causes diet change); requires literacy and motivation; may alter eating behaviour (reactivity); expensive to process; 3 days minimum; 7 days preferred for	Research studies requiring high accuracy; outpatient clinical assessment in motivated patients; establishing baseline intake before nutrition intervention; clinical dietetic practice in stable outpatients

			capturing weekend variation	
Dietary History	Structured interview exploring habitual dietary patterns, meal timing, food preferences, cooking methods, food allergies, and recent dietary changes — typically covering the past month	Captures habitual patterns and diet quality beyond nutrient numbers; reveals barriers (food avoidance, eating environment, cultural practices); efficient use of consultation time; builds therapeutic relationship	Relies on patient's ability to recall and describe habits accurately; not standardized; no quantitative output without follow-up recalls or diary; interviewer training essential	Clinical assessment of all patients; essential for understanding why a patient's intake is inadequate, not just what they eat; identifying appropriate counselling targets
Food record (observational)	Trained observer records all food consumed by a patient or child — used in institutional settings (hospitals, schools, feeding programs)	Eliminates recall error and literacy barrier; useful for non-communicating patients, infants, and institutional monitoring	Labour-intensive; observer effect; feasible only in institutional settings	Hospital ward food intake monitoring; therapeutic feeding program monitoring; paediatric assessment when parent recall is unreliable
Plate waste method	Weight of food served minus weight of food remaining after eating	Objective; suitable for inpatients; does not require patient participation	Food waste estimation may not reflect nutrient intake from foods consumed in different proportions; supplements not captured	Hospital food intake monitoring; evaluating institutional meal acceptance
Biomarkers of dietary intake	Objective biological measurements reflecting specific dietary exposures: urinary sodium/nitrogen (sodium and protein intake); plasma carotenoids (fruit/vegetable intake); plasma omega-3 index (fatty fish intake); urinary flavonoid metabolites (polyphenol intake)	Not subject to reporting bias; complement self-report methods; used in validation studies	Reflect recent intake only (most have short half-life); affected by absorption variation; expensive; not practical for routine clinical use	Validation of self-report dietary tools; research studies requiring objective dietary exposure data

PRACTICE

In clinical nutrition practice, the dietary assessment approach should match the clinical question. For a hospitalized patient: a brief dietary history + plate waste observation is most practical. For an outpatient with a chronic condition: 3-day food diary + dietary history interview gives the best picture. For population-level surveillance: 24-hour recall (multiple passes) or FFQ. The goal is not perfect data — it is actionable data: enough to identify the nature and magnitude of the problem and guide a targeted intervention.

E — Environmental, Social & Psychological Factors

The Determinants Behind the Dietary Data

The E domain Recognize s that nutritional status is determined not just by what a patient eats, but by the complex social, economic, psychological, and environmental determinants that shape their food choices and access. Without assessing and addressing these factors, dietary advice alone is insufficient.

Factor	Key Questions to Ask	Nutritional Implications & Interventions
Food security and access	Can the patient consistently access enough food? Do they have enough money for food? Are there food deserts or supply chain barriers in their area?	Food insecurity is a structural cause of malnutrition that requires systemic solutions alongside clinical ones. Identify: eligibility for food assistance programs; community food banks; social work referral. In Sudan: WHO/WFP food distribution access; community-based management of acute malnutrition (CMAM) program eligibility.
Cooking ability and food preparation	Can the patient prepare their own meals? Do they have access to cooking facilities? Do they have kitchen skills?	Elderly, physically disabled, mentally ill, or homeless patients may be unable to prepare nutritious food even if it is available. Interventions: meal delivery services; community kitchens; simplified recipe guidance; ready-to-eat therapeutic foods (RUTF for SAM management).
Social eating environment	Does the patient eat alone? Do they have family or social support around meals? Is meal socialization affected?	Eating alone is associated with reduced food intake and increased malnutrition risk in elderly adults. Social meals increase intake. Consider: family counselling; shared meal programs.
Psychological and mental health factors	Depression, anxiety, grief, loneliness, eating disorders, dementia, cognitive decline, substance use	Depression reduces appetite motivation. Anxiety causes GI symptoms that impair intake. Eating disorders require specialist psychological co-management. Cognitive decline impairs meal planning, shopping, and cooking ability. Screen with validated tools (GDS-15 for elderly depression; DEPS for eating disorders).
Cultural, religious, and personal food beliefs	Are there religious dietary restrictions (halal, kosher,	Dietary recommendations that violate cultural or religious practices will not be followed. A halal diet,

	fasting)? Cultural food preferences? Strong food dislikes or aversions?	for example, excludes pork products — directly relevant to protein supplement formulation in Muslim patients. Ramadan fasting in diabetes requires specific management. Understand the patient's food culture before prescribing.
Knowledge and nutrition literacy	Does the patient understand basic nutrition concepts? Do they understand their diagnosis and dietary requirements? Are they health literate?	Low health literacy is associated with poorer adherence to dietary advice. Use plain language, visual aids, and teach-back methods. Translate materials into the patient's preferred language. Avoid dietary jargon (e.g., say 'protein foods like meat, eggs, and beans' rather than 'adequate dietary protein intake').
Physical ability to eat	Are there dental problems? Dysphagia? Parkinson's tremor? Stroke-related feeding difficulties? Severe fatigue?	Physical barriers to eating may require: texture modification (minced, mashed, puree diets); thickened fluids for dysphagia; adaptive eating aids; positioning support; assisted feeding. SLT referral for dysphagia assessment.

PART FOUR — Diagnosing Malnutrition: The GLIM Criteria

The Global Leadership Initiative on Malnutrition (GLIM) criteria represent the first global consensus-based framework for diagnosing malnutrition in adults. Published in 2018 and endorsed by ESPEN, ASPEN, FELANPE, PENSA, and APCEBN, GLIM provides a universal, internationally applicable malnutrition diagnosis standard.

GLIM diagnosis requires at least ONE phenotypic criterion AND at least ONE aetiologic criterion:

Criterion Type	Criterion	Diagnostic Threshold
PHENOTYPIC (what the body shows)	1. Unintentional weight loss	5–10% in past 6 months (moderate); >10% in past 6 months (severe); or >20% in >6 months (severe)
PHENOTYPIC	2. Low BMI	≥20 years: <20 kg/m ² (moderate) or <18.5 (severe); >70 years: <22 kg/m ² (moderate) or <20 (severe); Asian populations: adjust thresholds downward per ethnic cut-offs
PHENOTYPIC	3. Reduced muscle mass	Low by validated measurement (DEXA, BIA, CT, anthropometry); ALMI: <7.0 kg/m ² men / <5.5 kg/m ² women (DEXA); or MUAC / calf circumference below sex-specific thresholds
AETIOLOGIC (the cause)	1. Reduced food intake or assimilation	≤50% of estimated requirements for >1 week; or any reduction for >2 weeks; or any chronic GI condition causing malabsorption or impaired assimilation
AETIOLOGIC	2. Disease burden / inflammation	Acute disease or injury (e.g., major infection, burns, trauma, surgery); or chronic disease-related (e.g., cancer, COPD, CKD, heart failure, IBD, HIV/AIDS) causing chronic or recurrent mild-to-moderate inflammation

GLIM Severity Staging	Criteria
Moderate malnutrition	One phenotypic criterion at moderate threshold
Severe malnutrition	One phenotypic criterion at severe threshold

CONNECT

GLIM vs MUST/NRS-2002: Screening tools (MUST, NRS-2002) identify patients at risk and trigger assessment. GLIM is a diagnostic framework — it confirms the presence and severity of malnutrition after assessment. A patient who screens positive with MUST and is then assessed using the ABCDE framework may be diagnosed as having moderate or severe malnutrition using GLIM criteria. The GLIM diagnosis is what drives the nutrition care plan, resource allocation, and clinical documentation.

PART FIVE — The Nutrition Care Process and ADIME Documentation

The Nutrition Care Process (NCP), developed by the Academy of Nutrition and Dietetics, provides a systematic framework for dietitians to deliver consistent, high-quality nutrition care. The ADIME format — Assessment, Diagnosis, Intervention, Monitoring and Evaluation — is the documentation structure that implements the NCP in clinical practice.

The ADIME Framework

Assessment → Diagnosis → Intervention → Monitoring & Evaluation

ADIME Component	Content	Key Elements & Examples
A — Assessment	Summaries all relevant data collected across the ABCDE domains	Anthropometric data (weight, height, BMI, % weight loss, MUAC, grip strength); Biochemical data (with interpretation in context of inflammation, hydration, organ function); Clinical data (medical history, medications, physical signs, functional status, screening score); Dietary data (recent intake, dietary history, appetite, intake vs requirements); Environmental/social factors (food security, cooking ability, social support, cultural factors)
D — Diagnosis (Nutrition Diagnosis)	State the specific nutritional problem using the PES format: Problem — Etiology — Signs and Symptoms	Format: 'Inadequate oral food and beverage intake (NI-2.1) related to reduced appetite and nausea secondary to chemotherapy as evidenced by 3-day food record showing 45% of estimated requirements and 8% unintentional weight loss in the past month.' The GLIM malnutrition diagnosis (moderate/severe) can be stated here alongside the PES statement.
I — Intervention	The specific nutritional actions planned and implemented	Energy prescription (kcal/day and basis); Protein prescription (g/kg/day and basis); Micronutrient supplementation; Route of feeding (oral, enteral, parenteral); Specific food or formula recommendations; Nutrition education and counselling topics; Referrals (SLT for dysphagia, social work for food insecurity, psychology for eating disorder); Coordination with medical team
M&E — Monitoring and Evaluation	Define what will be measured to assess progress, when, and target values	Specific measurable indicators: weight (target weight gain or maintenance); dietary intake (% of requirements met); biochemical markers (with frequency); functional measures (grip strength, SPPB); tolerance of nutrition support; patient-reported outcomes (appetite, quality of life); reassessment timeline

The PES Statement — Writing the Nutrition Diagnosis

The PES (Problem-Etiology-Signs and Symptoms) statement is the specific language used to document the nutrition diagnosis. It follows a standardized structure from the IDNT (International Dietetics and Nutrition Terminology) reference manual.

PES Component	Definition	Guidance
P — Problem (Nutrition Diagnosis Label)	The specific nutrition problem identified from the Nutrition Diagnosis taxonomy (IDNT)	Select from standardized taxonomy categories: NI (Nutritional Intake); NC (Nutrition Clinical); NB (Nutrition Behavioural/Environmental). Examples: Inadequate energy intake (NI-1.4); Malnutrition (NC-4.1.1 moderate / NC-4.1.2 severe); Unintended weight loss (NC-3.2); Swallowing difficulty (NC-1.1); Food-medication interaction (NC-2.3); Disordered eating pattern (NB-1.5).
E — Etiology (Related to...)	The root cause or contributing factor for the nutrition problem	Use 'related to' connector. Should identify the modifiable cause that the dietitian's intervention targets. Examples: 'related to nausea and vomiting secondary to chemotherapy'; 'related to dysphagia following stroke'; 'related to inadequate financial resources for food purchase'; 'related to voluntary food restriction consistent with disordered eating'.
S — Signs & Symptoms (As evidenced by...)	The objective and subjective data that confirm the nutrition problem exists	Use 'as evidenced by' connector. Should include quantified data: 'as evidenced by 3-day food record showing 40% of estimated energy requirements, 9% unintentional weight loss in 3 months, BMI 17.2 kg/m ² , and grip strength 11 kg'.

PRACTICE

A well-written PES statement enables any qualified dietitian who has not met the patient to understand the nature of the problem, its cause, and the evidence for it — in one or two sentences. Avoid vague statements like 'patient has poor nutrition.' Instead: 'Inadequate oral energy and protein intake (NI-1.4, NI-5.7.1) related to severe anorexia and early satiety secondary to gastroparesis, as evidenced by 24-hour recall showing 28% of estimated energy requirements (420 kcal vs 1500 kcal target) and unintentional weight loss of 12% over 2 months.'

PART SIX — Population-Level Nutritional Assessment

Individual clinical assessment addresses one patient at a time. Population-level nutritional assessment surveys the nutritional status of a community, region, or country — identifying the prevalence of malnutrition, tracking trends over time, targeting interventions, and evaluating program effectiveness. This is the domain of public health nutrition and is particularly critical in Sudan and similar settings experiencing protracted conflict, displacement, and food insecurity.

Population Indicators and Survey Methods

From Community Surveys to National Monitoring Systems

Indicator	What It Measures	Target Population	Threshold Significance
Global Acute Malnutrition (GAM)	Wasting: weight-for-height Z-score (WHZ) <-2 OR MUAC <125 mm in children 6–59 months	Children under 5	$<5\%$: acceptable; 5–10%: poor; 10–15%: serious; $>15\%$: critical (emergency response threshold). GAM $>15\%$ triggers humanitarian response.
Severe Acute Malnutrition (SAM)	WHZ <-3 OR MUAC <115 mm OR bilateral pitting oedema	Children under 5	SAM prevalence $>2\%$: serious; $>3\%$: critical. Requires inpatient or community-based therapeutic feeding.
Stunting prevalence	Height-for-age Z-score (HAZ) <-2 (low height for age = chronic undernutrition)	Children under 5	Reflects long-term nutritional deficiency, repeated illness, and food insecurity. $>40\%$: very high; 30–40%: high. In Sudan, stunting rates exceed 40% in many states.
Underweight prevalence	Weight-for-age Z-score (WAZ) <-2 (summary indicator of acute + chronic)	Children under 5	Widely used for MDG/SDG tracking; combines stunting and wasting effects.
Mid-Upper Arm Circumference (MUAC) <125 mm	Proxy for SAM in field settings (replaces anthropometric measurement when scales/length boards unavailable)	Children 6–59 months, pregnant women, adults	Primary admission criterion for CMAM programs. MUAC-based programs identify different children than WHZ-based, increasing coverage.

Infant and Young Child Feeding (IYCF) indicators	Exclusive breastfeeding rate (0–6 months); timely introduction of complementary foods (6 months); minimum dietary diversity (MDD); minimum meal frequency (MMF)	Infants and children 0–23 months	WHO recommends exclusive breastfeeding for 6 months + complementary feeding with continued breastfeeding to 2 years. Low EBF rates and poor complementary feeding are primary drivers of child stunting and wasting.
Maternal malnutrition indicators	MUAC <230 mm in pregnant women; BMI <18.5 pre-pregnancy; anaemia prevalence (Hb <110 g/L in pregnancy)	Pregnant and lactating women	Maternal malnutrition causes low birth weight, preterm birth, and intergenerational undernutrition. A malnourished mother is likely to give birth to a malnourished child.
Micronutrient deficiency indicators	Anaemia prevalence (Hb level by population); serum retinol (<0.7 µmol/L for VAD); urinary iodine concentration (UIC <100 µg/L for iodine deficiency); serum ferritin (<15 µg/L for iron depletion)	Age- and sex-specific population groups	VAD affects >30% of children under 5 in Sub-Saharan Africa. Iodine deficiency affects populations in inland Sudan far from iodized salt supply chains. Iron deficiency anaemia affects >40% of pregnant women in Sub-Saharan Africa.

CONTEXT

Sudan's nutritional crisis in context: Sudan's S3M II survey (2018) and subsequent emergency surveys have documented: GAM rates >15% in multiple states (Darfur, Blue Nile, South Kordofan); stunting rates >40% nationally; VAD affecting over 30% of children under 5; widespread anaemia in women of reproductive age. The 2020 FMOH-WFP Annual Work Plan identified the Double Burden of Malnutrition — coexisting undernutrition (particularly in children and rural populations) alongside rapidly rising obesity and non-communicable disease risk (particularly in urban populations) — as the defining nutritional challenge of Sudan's transition. Assessment systems must capture both ends of this spectrum.

Survey Method	What It Measures	Key Features	Use Case
SMART Survey (Standardized Monitoring and Assessment of Relief and Transitions)	GAM, SAM, stunting, underweight prevalence; crude mortality rate; IYCF indicators	Cluster-random sampling; standardized protocols; 450–900 child sample; internationally comparable results; mortality survey component	Gold standard for emergency nutritional assessment. Deployed in Sudan, South Sudan, Yemen, DRC, and other crisis settings. Results trigger humanitarian response.
SQUEAC/SLEAC	Coverage of CMAM program (Simplified LQAS Evaluation of Access and Coverage)	Rapid coverage assessment methods; SLEAC for program-level pass/fail; SQUEAC for in-depth coverage and barrier analysis	Evaluating whether therapeutic feeding programs are reaching children who need them; identifying barriers to access.
Demographic and Health Survey (DHS)	Household survey: child nutrition, maternal nutrition, IYCF, anaemia, micronutrient status across nationally representative sample	5-year cycle; large nationally representative sample (5,000–15,000 households); gold standard for national trend data	National nutrition trend monitoring; SDG and global nutrition target tracking; sector planning.
National Micronutrient Survey	Prevalence of specific micronutrient deficiencies (vitamin A, iron, iodine, zinc) in target population groups	Biomarker collection (blood, urine); representative sample; requires laboratory infrastructure	Informing national micronutrient supplementation and fortification programs; evaluating intervention impact.

Clinical Scenario: Integrated Case: Hana, 67 Years Old, Port Sudan

- Hana is a 67-year-old woman referred to the outpatient nutrition clinic by her physician. Her presenting complaint is fatigue and unintentional weight loss over the past 4 months. She has a background of type 2 diabetes (on metformin 1g twice daily), hypertension (on amlodipine 5mg), and osteoarthritis of both knees. She lives alone since her husband's death 6 months ago. She says her appetite has reduced significantly, she has difficulty preparing food due to her knee pain, and she often skips meals because she has 'no reason to cook for one person.'
- On examination: Height 158 cm; Current weight 52 kg (reported usual weight 62 kg 6 months ago); BMI 20.8 kg/m²; MUAC 21 cm; Calf circumference 28 cm; Grip strength 13 kg (dominant hand). Physical signs: pallor of conjunctiva; angular cheilitis; thinning temporal muscles; mild bilateral ankle oedema.
- Biochemistry: Hb 98 g/L; MCV 74 fL; Serum iron 6 µmol/L; TIBC elevated; Ferritin 8 µg/L; Albumin 28 g/L; CRP 14 mg/L; Pre-albumin 160 mg/L; Serum B12 180 pmol/L; Serum 25(OH)D 28 nmol/L; Fasting glucose 9.1 mmol/L; HbA1c 8.4%.
- Brief dietary history: 2 meals per day (porridge at breakfast, rice with minimal additions in the evening); no meat, fish, or eggs in past 3 months ('too expensive and too much effort to cook'); occasional flatbread with dates. No fruit or vegetables. Tea with every meal.
- Question 1: Apply the MUST screening tool. What score does Hana receive, and what action does this trigger? Then apply the NRS-2002. What additional information does NRS-2002 capture that MUST misses for this patient?
- Question 2: Systematically work through the ABCDE assessment. For each domain, list the key abnormal findings and interpret their nutritional significance.
- Question 3: Interpret the biochemical results in full context. For each abnormal marker, explain the most likely cause and what additional information would help confirm your interpretation. How does the concurrent CRP affect your interpretation of the albumin and pre-albumin?
- Question 4: Apply the GLIM criteria. What phenotypic and aetiologic criteria are met? What is Hana's GLIM malnutrition diagnosis (moderate or severe)?
- Question 5: Write a complete PES statement for Hana's primary nutrition diagnosis. Then draft the I (Intervention) and M&E (Monitoring and Evaluation) components of an ADIME note for her first clinic visit.

Critical Thinking Questions

- The lecture describes albumin as a poor marker of nutritional status in inflamed or acutely ill patients — yet it remains one of the most frequently cited nutrition indicators in clinical documentation. What are the consequences of this practice? How would you, as a clinical dietitian, communicate this limitation to a medical colleague who has documented 'albumin 22 g/L — severe hypoproteinaemia, nutritional support required' without assessing dietary intake or CRP?

- Nutritional screening tools like MUST and NRS-2002 were developed and validated primarily in European hospital populations. When used in Sudanese or East African clinical settings, what adaptation might be needed to maintain their validity? Which components are likely to be most problematic (e.g., BMI measurement challenges, different background rates of malnutrition, different disease distributions)?
- The E domain of the ABCDE assessment captures social, economic, and environmental determinants of nutritional status — factors that a clinical dietitian cannot change through dietary advice alone. How should clinical nutrition practice engage with structural determinants of malnutrition (poverty, food insecurity, conflict, displacement)? What is the dietitian's role at the interface between individual clinical care and population-level food systems advocacy?

Lecture Summary — Key Takeaways for Dietetic Practice

- Screening vs Assessment: Screening (2–5 min, any trained staff) identifies at-risk patients using validated tools (MUST, NRS-2002, MNA). Assessment (30–60 min, dietitian) comprehensively characterises malnutrition across ABCDE domains. Both steps are necessary; neither replaces the other.
- Screening tools: MUST (3 components: BMI, % weight loss, acute disease effect; scores 0–2+; any adult, any setting). NRS-2002 (adds disease severity score; recommended by ESPEN for hospital inpatients; better captures catabolic drive of serious illness). MNA-SF (older adults; includes calf circumference alternative to BMI; 6 items). PG-SGA (gold standard for oncology).
- ABCDE Assessment: A = Anthropometry (weight history, BMI, MUAC, grip strength, growth charts for children). B = Biochemistry (albumin + CRP together — never albumin alone; pre-albumin; Hb + MCV; iron indices; vitamin D; electrolytes). C = Clinical (medical history; drug-nutrient interactions; physical signs by body system; functional status including grip strength). D = Dietary (24h recall, FFQ, food diary, dietary history, plate waste — match method to clinical question). E = Environmental (food security, cooking ability, social isolation, mental health, cultural factors, health literacy).
- Biochemical interpretation: Albumin is a negative acute-phase reactant — low albumin in hospital primarily reflects inflammation, not protein depletion. Always interpret alongside CRP. Ferritin is a positive acute-phase reactant — elevated ferritin does not exclude iron deficiency in inflamed patients. Serum zinc is insensitive — falls with inflammation regardless of zinc status. No single biomarker diagnoses malnutrition; panels interpreted in clinical context are required.
- GLIM Malnutrition Diagnosis: Requires at least 1 phenotypic criterion (weight loss $\geq 5\%$; BMI < 20 or age-adjusted cut-off; low muscle mass) AND at least 1 aetiologic criterion (reduced intake/assimilation; disease burden/inflammation). Staging: moderate vs severe based on phenotypic threshold severity.
- ADIME Documentation: Assessment (ABCDE data summary) → Diagnosis (PES statement: Problem related to Etiology as evidenced by Signs and Symptoms; use IDNT terminology) → Intervention (energy/protein targets, route, education, referrals) → Monitoring & Evaluation (specific indicators, frequency, targets). PES statements must be specific, quantified, and actionable.
- Population assessment: SMART survey for emergency settings (GAM, SAM, stunting prevalence); SQUEAC/SLEAC for CMAM program coverage; DHS for national trend data. Key Sudan indicators: GAM

>15% in multiple states; stunting >40% nationally; VAD in >30% of children; Double Burden (coexisting undernutrition + rising obesity/NCD). MUAC-based screening is the primary field tool for SAM detection and CMAM admission across Sudan.

Suggested reading:

1. Kondrup J et al. (2003). ESPEN guidelines for nutrition screening 2002. Clinical Nutrition. |
2. Cederholm T et al. (2019). GLIM criteria for the diagnosis of malnutrition. Clinical Nutrition. |
3. Gibson RS (2005). Principles of Nutritional Assessment, 2nd Ed. — the definitive reference for dietary and biochemical assessment methods. |
4. Academy of Nutrition and Dietetics (2021). International Dietetics and Nutrition Terminology (IDNT) Reference Manual, 5th Ed. |
5. WHO (2021). Training Course on Child Growth Assessment. |
6. Vellas B et al. (2006). The Mini Nutritional Assessment (MNA) and its use in grading the nutritional state of elderly patients. Nutrition.

Module 4 — Oxidative Stress, Phytochemicals & Functional Foods

A 3-Lecture Graduate Series: Free Radicals & Antioxidants • Phytochemicals • Fruits & Vegetables

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Free Radicals & Antioxidant Defense

Biochemical Mechanisms, Chronic Disease Pathways & Therapeutic Strategies

- ▶ Part 1: What Are Free Radicals and Why Do They Form?
- ▶ Part 2: How Free Radicals Damage the Body — Lipids, Proteins, DNA & AGEs
- ▶ Part 3: The Antioxidant Defense System — Enzymatic, Glutathione & Nrf2 Pathway
- ▶ Part 4: Oxidative Stress in Chronic Disease — CVD | Cancer | Type 2 Diabetes
- ▶ Part 5: Why Antioxidant Supplements Fail While Dietary Patterns Succeed
- ▶ Part 6: Practical Guidance — Dietary Strategies & Lifestyle Factors
- ▶ Clinical Case: Ahmed — Diabetic Teacher, Khartoum & Oxidative Stress Management

Oxidative Stress & Free Radicals

A Clinical Reasoning Approach: What Damages Cells, Why the Body Defends Itself, and When Diet Makes the Difference

Focus: Understanding mechanisms of cell damage and antioxidant defesce — not memorising chemical equations

The Central Question: Why Does the Body Need Antioxidant Protection?

Every cell in the body continuously produces unstable, highly reactive molecules as a natural byproduct of being alive. These molecules — free radicals and reactive oxygen species — damage whatever they contact: cell membranes, proteins, DNA, and the proteins that carry cholesterol in the bloodstream. The body has a sophisticated defesce system to neutralize this damage. When that balance tips — when reactive species overwhelm the defesce — the result is oxidative stress, which contributes to the development and progression of cardiovascular disease, cancer, type 2 diabetes, neurodegenerative diseases, and accelerated ageing.

WHY?

This lecture builds on a simple but profound question: why do fruits, vegetables, nuts, and whole grains protect against chronic disease? Part of the answer lies here — in the antioxidant defesce they support. Understanding oxidative stress does not require memorizing chemical equations. It requires understanding what goes wrong when cells are chronically overwhelmed, and what dietary patterns prevent that.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain in plain terms what a free radical is, where free radicals come from, and why they are dangerous to cells
- Describe the four major targets of oxidative damage — fats, proteins, DNA, and glucose — and connect each to a clinical consequence
- Explain how the body's antioxidant defesce system works and identify the key nutrients that keep it functioning
- Connect oxidative stress to the actual disease processes of cardiovascular disease, cancer, and type 2 diabetes
- Explain why antioxidant supplements have largely failed in clinical trials while dietary patterns succeed — and apply this to patient counselling
- Describe the lifestyle and dietary factors that increase oxidative stress — and those that reduce it

PART ONE — What Are Free Radicals and Why Do They Form?

A free radical is simply a molecule that has lost an electron and is urgently trying to steal one back from a neighboring molecule. When it does, that neighbor also becomes unstable and steals from its neighbor — and a chain reaction of damage begins. The body produces free radicals every second as an unavoidable consequence of normal metabolism, but also acquires them from the environment through smoking, air pollution, radiation, and the food we eat.

Where Free Radicals Come From

Endogenous Production vs. Environmental Exposure

Inside the Body — The Unavoidable Sources

The largest source of free radicals in the human body is the mitochondria — the energy factories in every cell. When cells convert food into ATP (energy), the process is not perfectly clean: a small percentage of electrons escape the process and react with oxygen to form superoxide, the first and most important free radical. The more actively a cell is generating energy, the more free radicals it produces as a byproduct.

Source Inside the Body	What It Produces	Clinical Relevance
Mitochondria (energy production)	Superoxide — produced continuously during normal metabolism; the primary endogenous source	Every tissue that uses energy produces free radicals. More metabolically active tissues (heart, liver, skeletal muscle during exercise) produce more. This is why ageing — accumulated mitochondrial damage — is inseparable from oxidative stress.
Immune cells during infection	A deliberate burst of free radicals to kill bacteria and viruses (the 'respiratory burst')	This is beneficial in the short term — the immune system uses oxidants as weapons. But chronic infections, chronic inflammation, or autoimmune conditions produce persistent oxidative stress that damages the body's own tissues.
Liver during drug and alcohol metabolism	The liver's detoxification enzymes generate free radicals as a byproduct of processing drugs, alcohol, and environmental chemicals	This is why heavy alcohol use, frequent medication use, and occupational chemical exposure accelerate oxidative damage — the liver is working hard to detoxify, generating substantial free radicals in the process.
Iron and copper when unbound	These metals catalyze the formation of the most dangerous free radical (hydroxyl radical) from hydrogen peroxide	This is why iron overload conditions (haemochromatosis), repeated blood transfusions, and dysregulated iron metabolism amplify oxidative damage. Free iron in tissues is a pro-oxidant — this is also why iron supplementation requires careful clinical judgement.

From Outside the Body — Environmental Sources

External Source	Mechanism	Magnitude of Impact
Cigarette smoke	Each puff contains approximately 100 trillion free radical molecules directly, plus compounds that trigger the body to produce its own. Simultaneously depletes vitamin C and other antioxidants.	The single largest modifiable source of oxidative stress. A smoker's antioxidant requirement for vitamin C alone is 35mg/day higher than a non-smoker — yet smokers typically consume less vitamin C from diet.
Air pollution (PM2.5 fine particles)	Fine particulate matter from traffic, industry, and cooking fires triggers free radical production in the lung lining and stimulates a continuous low-grade immune response	Particularly relevant in urban Sudan and Sub-Saharan Africa where indoor cooking fires and traffic pollution are significant. Associated with cardiovascular and respiratory disease independently of diet.
Ultraviolet radiation (sunlight)	UV radiation generates free radicals directly in skin cells, damaging DNA — the primary cause of skin cancer	Protective effect of carotenoids in skin (beta-carotene, lycopene, astaxanthin) is partly mediated by quenching these radiation-generated free radicals
Processed and fried foods	Oxidized fats in fried and ultra-processed foods, plus advanced glycation end products (AGEs) formed during high-heat cooking, are absorbed and directly contribute to the body's oxidative burden	This is one of the key mechanisms by which ultra-processed food patterns damage health — not just through calories, sodium, and sugar, but through the direct pro-oxidant load they deliver.
Chronic psychological stress	Stress hormones stimulate free radical production via activation of immune and metabolic pathways	Connects psychosocial stress to biological disease mechanisms — relevant for understanding why chronic stress is a genuine cardiovascular and cancer risk factor, not merely a quality-of-life issue.

CONNECT

The most important insight about free radical sources: they are cumulative. A person who smokes, eats a highly processed diet, is exposed to indoor cooking smoke, carries chronic stress, and has poorly controlled diabetes is experiencing free radical production from five simultaneous sources. Their antioxidant defense system is overwhelmed by volume, not by any single exposure. This is why dietary pattern — not individual nutrients — is the relevant unit of analysis.

PART TWO — How Free Radicals Damage the Body

Free radicals do not discriminate. They damage whatever molecule is nearest to them when they are formed. In practice, four types of molecules are most frequently and consequentially damaged: fats (especially in cell membranes and blood), proteins (especially enzymes and structural proteins), DNA, and glucose-modified proteins (glycation). Each type of damage connects to specific clinical consequences.

The Four Targets of Oxidative Damage

Fats, Proteins, DNA & Sugar-Modified Proteins

Target 1 — Cell Membrane Fats and LDL Cholesterol

Cell membranes are built from polyunsaturated fatty acids (PUFAs) — the same healthy fats found in fish, nuts, and plant oils. PUFAs are particularly vulnerable to free radical attack because of their chemical structure. When a free radical attacks a PUFA in a cell membrane, it starts a chain reaction called lipid peroxidation — each damaged fat molecule damages the next, like a row of falling dominoes.

WHY?

This explains why LDL cholesterol oxidation is central to cardiovascular disease. LDL particles transport cholesterol in the bloodstream. When their fat component is damaged by free radicals, the resulting 'oxidized LDL' is recognized as foreign by immune cells in the artery wall. These immune cells engulf the oxidized LDL and transform into 'foam cells' — the building blocks of atherosclerotic plaque. Normal LDL is not directly atherogenic; oxidized LDL is. This is why dietary patterns that reduce LDL oxidation (antioxidant-rich diets, olive oil, omega-3s) reduce cardiovascular disease risk beyond what cholesterol-lowering alone achieves.

Damage Product	What It Is	Clinical Connection
Oxidized LDL (oxLDL)	LDL particles whose fat component has been damaged by free radicals	Recognized by immune cells in artery walls → foam cells → atherosclerotic plaque → heart attack and stroke. Serum oxLDL is a cardiovascular risk biomarker. Mediterranean diet reduces oxLDL.
Malondialdehyde (MDA) and 4-HNE	Toxic breakdown products of fat peroxidation that form further adducts with DNA and proteins	Markers of oxidative stress measured in research. Elevated in CVD, T2DM, obesity, and smoking. Cause additional protein and DNA damage wherever they travel.
F2-isoprostanes	Formed when arachidonic acid (an omega-6 fat) is damaged by free radicals	The most reliable biomarker of in vivo oxidative stress. Measurable in urine and plasma. Elevated in smokers, CVD patients, diabetics, and the obese. Reduced by antioxidant-rich dietary patterns.

Target 2 — Proteins

Proteins are the working machinery of every cell — enzymes, structural components, receptors, hormones. When free radicals attack proteins, they deform their three-dimensional structure, which either inactivates enzymes or makes them attack the body's own tissues. Damaged proteins accumulate over time when the damage rate exceeds the cell's capacity to remove them.

Protein Damage Type	Consequence	Clinical Example
Carbonylation (protein 'rusting')	Irreversible modification of amino acids that marks the protein for destruction; accumulates when damage is chronic	Carbonylated proteins accumulate in ageing tissues, neurodegenerative diseases (Alzheimer's, Parkinson's), and COPD. The carbonyl content of a tissue is a measure of its cumulative oxidative damage history.
Tyrosine nitration (from peroxynitrite)	Permanently modifies signaling proteins; disrupts the normal cell communication that relies on protein phosphorylation	Peroxynitrite forms when superoxide reacts with nitric oxide. Elevated 3-nitrotyrosine is a marker of vascular disease and neurodegeneration. Connects oxidative and nitrosative stress.
Lens crystalline cross-linking	Structural proteins of the eye lens aggregate and lose transparency when oxidatively damaged	Cataracts — the world's leading cause of blindness — are partly an oxidative stress disease. Lutein and zeaxanthin (from leafy greens and egg yolk) accumulate in the lens and protect against this damage.

Target 3 — DNA

DNA damage by free radicals is the most consequential target — because DNA is the instruction manual for every protein the cell makes, and because DNA damage, if not repaired before cell division, can be permanently passed to daughter cells as a mutation. The body repairs approximately 10,000 to 100,000 oxidative DNA lesions per cell per day through dedicated repair systems.

WHY?

The connection between oxidative DNA damage and cancer is mechanistic: free radical attack on DNA in a tumour-suppressor gene converts a normal cell into one with a growth advantage. This is not random bad luck — it is a predictable consequence of chronic oxidative stress. This is why smokers, obese individuals, and people with chronic inflammation have higher cancer rates. It is also why people who eat antioxidant-rich diets have lower cancer rates — they are reducing the rate at which DNA is damaged.

DNA Damage Type	Mutagenic Consequence	Relevant Context
8-OHdG (8-hydroxydeoxyguanosine)	Causes G→T transversion mutations in proto-oncogenes; a hotspot in cancer-driver genes (KRAS, TP53). Gold standard biomarker of oxidative DNA damage — measurable in urine	Elevated in cancer patients, smokers, T2DM, and obese individuals. Reduced by Mediterranean diet and increased fruit/vegetable intake in intervention studies. The most clinically useful biomarker of oxidative stress exposure.
DNA strand breaks	Double-strand breaks can cause large-scale chromosomal rearrangements if repair fails	Ionising radiation and the hydroxyl radical (the most reactive free radical, produced from iron + hydrogen peroxide) are the primary causes. DNA double-strand breaks are the most cytotoxic DNA lesion.
Telomere shortening	Oxidative damage accelerates telomere loss, reducing the number of times a cell can divide before becoming senescent	Telomere length is a biological ageing marker. Mediterranean diet and reduced oxidative stress are associated with slower telomere shortening — a mechanism connecting dietary patterns to healthy longevity.

Target 4 — Sugar-Protein Glycation and AGEs

A fourth type of damage occurs when blood glucose reacts with proteins — not through free radicals directly, but accelerated by oxidative conditions. This process, called glycation, gradually damages long-lived proteins throughout the body. The end products, called Advanced Glycation End Products (AGEs), accumulate in tissues and activate inflammatory pathways.

Where AGEs Accumulate	What Goes Wrong	Clinical Consequence
Collagen in blood vessel walls	AGE cross-links stiffen collagen fibers → loss of vascular elasticity	Arterial stiffness — a direct contributor to hypertension and increased cardiac workload. Explains part of the CVD risk in diabetes independent of cholesterol levels.
Myelin sheath around nerves	AGE damage to myelin and nerve proteins impairs nerve conduction	Diabetic neuropathy — the tingling, numbness, and pain in feet and hands that affects many people with long-standing diabetes. The AGE-nerve connection is a key mechanism.
Lens proteins in the eye	AGE cross-links aggregate lens proteins → opacity	Diabetic cataracts and accelerated lens clouding in people with chronic hyperglycaemia.
Glomerular proteins in the kidney	AGE damage to the kidney filter → progressive loss of function	Diabetic nephropathy — the leading cause of kidney failure requiring dialysis in most countries.

AGEs in Food		How They Form	What This Means in Practice
High-heat methods	cooking	Grilling, frying, baking at above 150°C generate AGEs in food; 10-40% of dietary AGEs are absorbed	Dietary AGEs add to the body's AGE burden — particularly relevant in people with diabetes, kidney disease, or chronic inflammation who already have impaired AGE clearance
Lower-heat methods	cooking	Boiling, steaming, poaching, and stewing generate far fewer AGEs from the same foods	Practical counselling: for patients with diabetes, CKD, or high cardiovascular risk, cooking method is a genuine nutritional intervention. Marinating meat in acidic liquids (lemon, vinegar) before grilling reduces AGE formation by approximately 50%.

PART THREE — The Body's Antioxidant Defense System

The body does not passively accept oxidative damage. It has evolved a sophisticated, multi-layered defense system to neutralize free radicals before they cause harm. This system has two arms: enzymatic (proteins built into cells that chemically dismantle free radicals) and non-enzymatic (molecules, many derived from diet, that sacrifice themselves to neutralize radicals). Both arms depend on adequate nutrition to function.

The Antioxidant Defense System

Enzymatic Defences, the GSH Network, and Dietary Antioxidants

The Enzymatic Defense — First Line

The body's enzymatic antioxidants are the primary, most powerful defense — operating continuously, catalytically, converting millions of free radical molecules per second without being consumed themselves. Their limiting factor is the cofactor minerals they require.

Enzyme		Its Job	The Mineral It Needs	What Deficiency Causes
Superoxide (SOD)	Dismutase	Converts superoxide (the primary free radical produced by mitochondria) into the less reactive hydrogen peroxide	Manganese (in mitochondria), Copper + Zinc (in cytoplasm)	Manganese, copper, or zinc deficiency reduces the body's first line of defense against the most abundant cellular free radical — increasing oxidative damage to mitochondria and cytoplasm
Catalase		Converts hydrogen peroxide (the product of SOD) into water and	Iron (as haem)	Impaired catalase activity allows hydrogen peroxide

	oxygen — completing the detoxification		to accumulate, where it can react with free iron to produce the most destructive radical (hydroxyl radical). Relevant in iron dysregulation conditions.
Glutathione Peroxidase (GPx)	Neutralizes both hydrogen peroxide AND damaged fat molecules in membranes — the enzyme that protects cell membranes from lipid peroxidation	Selenium (as selenocysteine)	Selenium deficiency impairs GPx activity → reduced protection against membrane fat damage and hydrogen peroxide → increased cardiovascular and cancer risk. The selenium-GPx link is why selenium-deficient regions have higher cardiomyopathy rates (Keshan disease).
Glutathione Reductase (GR)	Regenerates glutathione (the cell's master antioxidant molecule) from its oxidized form — keeps the antioxidant cycle running	Riboflavin (Vitamin B2)	Riboflavin deficiency impairs the regeneration of glutathione — connecting the B vitamin status to antioxidant defense capacity. One more reason why riboflavin is a gateway nutrient.

CONNECT

The mineral cofactors for antioxidant enzymes are the most direct link between mineral nutrition and oxidative protection. Selenium for GPx; manganese, copper, zinc for SOD; riboflavin for GR. This is why micronutrient adequacy — not just antioxidant supplement intake — is the foundation of antioxidant defense. A selenium-deficient person cannot produce adequate GPx regardless of how many antioxidant supplements they take.

Glutathione — The Master Intracellular Antioxidant

Glutathione (GSH) is a small molecule found in high concentrations inside virtually every cell in the body. It serves as the ultimate electron donor — sacrificing itself to neutralize a wide range of free radicals and toxic molecules, and then being regenerated by glutathione reductase (using riboflavin) to neutralize the next threat. The GSH:GSSG ratio (reduced to oxidized glutathione) is the most sensitive measure of a cell's redox status.

WHY?

Glutathione cannot be effectively supplemented orally — it is broken down in the gut before it can enter cells. The clinically effective approach is to support the body's own GSH synthesis by providing its precursors: cysteine (from protein-rich foods, or as N-acetylcysteine supplement), glutamate, and glycine. Dietary patterns rich in sulphur-containing amino acids (from meat, eggs, allium vegetables, cruciferous vegetables) support GSH synthesis. This is one of the mechanisms by which animal protein intake contributes to antioxidant status.

Condition or Factor	Effect on Glutathione	Clinical Significance
Acetaminophen (paracetamol) overdose	Depletes GSH catastrophically — liver GSH is consumed neutralizing the toxic metabolite NAPQI	The primary mechanism of acetaminophen liver toxicity. N-acetylcysteine (a cysteine prodrug) is the antidote — it replenishes GSH to prevent liver failure. The most dramatic clinical illustration of GSH's protective role.
Alcohol use disorder	Chronically depletes GSH through multiple mechanisms — increased oxidative stress, impaired synthesis, and direct GSH consumption by alcohol metabolites	Low GSH is a key mechanism of alcoholic liver disease. NAC is used adjunctively in some protocols. Dietary cysteine sources (from whey protein, eggs, garlic) may offer partial support.
HIV/AIDS	Dramatic depletion of GSH, particularly in T lymphocytes — contributes to immune dysfunction beyond CD4 cell count decline alone	GSH depletion may partly explain immune dysfunction disproportionate to viral load. Nutritional support for GSH synthesis is a component of nutritional care in HIV.
Critically ill patients (ICU)	GSH depletion is universal in critical illness — magnitude correlates with severity and mortality	IV glutathione precursors (NAC, cysteine) are used in some intensive care protocols. Nutritional assessment of antioxidant status is relevant in the ICU but often overlooked.

The Nrf2 Switch — How the Cell Turns On Its Own Defense

The body does not just use antioxidants passively. It has a master switch — a protein called Nrf2 — that detects when oxidative stress is rising and responds by activating over 200 genes that produce antioxidant enzymes, detoxification proteins, and GSH synthesis machinery. Understanding Nrf2 is key to understanding why certain plant foods are so powerfully protective.

The Nrf2 System	How It Works	Dietary Connection
Under normal conditions	Nrf2 is held inactive in the cytoplasm by a 'keeper' protein called Keap1 — continuously being marked for destruction	The cell maintains a baseline level of antioxidant defences without overinvesting in it
Under oxidative stress	Keap1 is modified by reactive molecules → releases Nrf2 → Nrf2	The cell detects its own damage and responds by dramatically upregulating its

	travels to the nucleus → switches on over 200 protective genes	defenses — a self-amplifying protection system
Key genes switched on by Nrf2	Glutathione synthesis enzymes (GCL, GSS); glutathione peroxidase; heme oxygenase-1; NQO1 (detoxification); ferritin (iron sequestration); Phase II liver detoxification enzymes	Activating Nrf2 essentially upgrades the entire cellular antioxidant and detoxification system simultaneously — explaining why Nrf2 activators have broad protective effects
Dietary Nrf2 activators	Sulforaphane from broccoli/broccoli sprouts (most potent known dietary activator); curcumin (turmeric); quercetin (onions, kale); EGCG (green tea); allicin (garlic); lycopene (cooked tomatoes)	This is the molecular explanation for why these specific plant foods are so consistently associated with cancer prevention and chronic disease protection — they activate the body's own endogenous defense systems, not just scavenge individual free radicals

PRACTICE

The Nrf2 pathway explains one of the most important principles in nutrition counselling: the protective effect of plant foods comes primarily from activating the body's own defenses, not from directly neutralizing free radicals. This is why sulforaphane from broccoli sprouts is more powerful than vitamin C at the same dose — because it switches on hundreds of protective genes rather than scavenging individual molecules. Food patterns, not single nutrients, activate Nrf2 most effectively.

Dietary Antioxidants — The Non-Enzymatic Defense

Dietary antioxidants are molecules consumed in food that directly neutralize free radicals or support the enzymatic defense system. Unlike enzymes, they are consumed in the process — each antioxidant molecule neutralizes one or a few free radicals before being regenerated or excreted. The key principle is that they work as a network, regenerating each other — not as isolated agents.

Dietary Antioxidant	Where It Acts	Key Role	Regenerated by
Vitamin E (alpha-tocopherol)	Cell membranes and LDL particles — the lipid phase	Chain-breaking antioxidant that stops lipid peroxidation — donates a hydrogen atom to the lipid peroxyl radical and halts the damage chain reaction. The most important antioxidant for protecting cell membranes and LDL from oxidation.	Vitamin C regenerates vitamin E at the membrane-water interface — the primary example of antioxidant network synergy
Vitamin C (ascorbate)	Blood, tissue fluids, cytoplasm — the water phase	Primary water-phase antioxidant; scavenges free radicals in blood and tissue fluids; regenerates vitamin E; enhances non-haem iron absorption; required for collagen synthesis and several Nrf2-activating enzymes	Glutathione and the thioredoxin system regenerate ascorbate — GSH, B2, and selenium all connect back here

Carotenoids (beta-carotene, lycopene, lutein)	Cell membranes and lipoproteins — lipid phase	Specialized quenchers of singlet oxygen (a particularly damaging form of excited oxygen produced by UV radiation and immune cells). Concentrated in specific tissues: lutein and zeaxanthin in the retina, lycopene in the prostate, beta-carotene in the skin	Not regenerated — used up and replaced through dietary intake
Polyphenols from plant foods	Gut, blood, and tissues depending on absorption	Activate Nrf2 (indirect); directly scavenge radicals; chelate free iron and copper (preventing Fenton reaction); modulate inflammation; modify the gut microbiome to increase the body's overall antioxidant capacity	Many polyphenols increase the body's endogenous antioxidant enzyme expression via Nrf2 — effectively regenerating the defense system rather than just the molecule itself

CONNECT

The antioxidant network principle: Vitamin C regenerates Vitamin E. Glutathione (which requires riboflavin to regenerate) keeps vitamin C active. Selenium enables glutathione peroxidase. Polyphenols activate the synthesis of all these enzymes via Nrf2. This network means that a deficiency of any single component weakens the whole system. It also explains why isolated antioxidant supplements fail — they supplement one component of an integrated network, often disrupting the balance rather than enhancing it.

PART FOUR — Oxidative Stress in Chronic Disease

Understanding what goes wrong in specific diseases requires connecting the mechanisms of oxidative damage to the pathology of each condition. Three diseases are examined here because the evidence for oxidative stress as a contributing mechanism is strongest, and because dietary antioxidant protection in each is clinically meaningful.

Disease Connections

Cardiovascular Disease, Cancer & Type 2 Diabetes

Cardiovascular Disease — From Free Radical to Heart Attack

Atherosclerosis — the progressive narrowing and stiffening of arteries that causes most heart attacks and strokes — is fundamentally an inflammatory and oxidative process, not simply a problem of too much cholesterol. Oxidative stress drives every stage from the initial injury to final plaque rupture.

Stage of Disease	The Oxidative Mechanism	What This Means Clinically
Endothelial dysfunction (earliest stage)	Superoxide destroys nitric oxide (NO) — the molecule that keeps blood vessels relaxed and prevents platelets from sticking. Without NO, blood vessels become stiff and reactive.	Endothelial dysfunction is measurable before clinical disease by flow-mediated dilation (FMD) testing. Diet-related improvement in FMD after antioxidant-rich eating is a clinically meaningful endpoint. This is why hypertension begins at the cellular level before blood pressure rises.
LDL oxidation and foam cell formation	Free radicals damage LDL particles in the sub-endothelial space. Immune cells Recognize oxidized LDL as foreign → engulf it → become foam cells → fatty streak in artery wall.	Normal LDL is not directly atherogenic — oxidized LDL is. This is why the quality of the diet (its oxidative potential) matters for CVD risk beyond LDL level alone. Mediterranean diet, rich in antioxidants and MUFAs, reduces LDL oxidation.
Plaque growth and inflammation	Free radicals activate NF-kB in macrophages and endothelial cells → inflammatory molecules are produced → more immune cells recruited → plaque grows and becomes unstable.	Chronic low-grade inflammation (measurable as high-sensitivity CRP) reflects this ongoing NF-kB activation. Anti-inflammatory and antioxidant dietary patterns reduce hsCRP — a direct biomarker of plaque instability risk.
Plaque rupture and thrombosis	Oxidative stress weakens the fibrous cap of the plaque → rupture → thrombosis → acute MI or stroke.	This is the final, catastrophic event. Preceding decades of oxidative and inflammatory damage make the plaque vulnerable. Antioxidant dietary patterns reduce this vulnerability over time — not acutely, but through years of protection.

CONTEXT

The PREDIMED trial — one of the most important nutrition trials ever conducted — demonstrated a 30% reduction in major cardiovascular events with a Mediterranean diet enriched with extra-virgin olive oil or nuts. The mechanisms include reduced LDL oxidation, improved endothelial function, reduced inflammation, and reduced platelet aggregation — all mediated partly through antioxidant and anti-inflammatory plant bioactives. This is the most powerful evidence we have that dietary pattern change prevents heart disease.

Cancer — How Oxidative DNA Damage Initiates Malignant Transformation

Cancer is not caused by a single oxidative hit. It is the cumulative result of DNA damage, failed repair, clonal expansion of damaged cells, and eventual loss of growth control. Oxidative stress contributes to at least the first three of these stages.

Stage of Carcinogenesis	Oxidative Mechanism	Dietary Implication
Initiation — DNA mutation	Free radical attack on proto-oncogenes and tumor suppressor genes creates permanent mutations in dividing cells. The 8-OHdG lesion on guanine is the most common — and directly measurable — oxidative DNA mutation.	Higher dietary antioxidant intake is inversely associated with urinary 8-OHdG levels in prospective studies. Lower 8-OHdG = less mutation risk. Cruciferous vegetables (sulforaphane) upregulate DNA repair enzymes through Nrf2 activation.
Promotion — clonal expansion	ROS activate NF-κB and AP-1 transcription factors → pro-survival signals prevent apoptosis of damaged cells → the mutated clone expands. This stage can last years before clinical cancer.	Anti-inflammatory dietary patterns (Mediterranean, plant-based) reduce NF-κB activation and the inflammatory microenvironment that promotes clonal expansion. Quercetin, curcumin, resveratrol, and EGCG inhibit NF-κB in cell models and early clinical trials.
Progression — invasion and metastasis	Sustained oxidative stress destabilizes the genome further → additional mutations accumulate → the cancer becomes aggressive and capable of spreading.	High antioxidant dietary scores are inversely associated with cancer mortality in large cohort studies (EPIC, Nurses' Health Study). The effect is most consistent for upper GI, colorectal, and lung cancers — where dietary exposure to antioxidant-poor food patterns is most directly relevant.

PARADOX

The most important caution in this area: while antioxidant-rich diets protect against cancer initiation and early promotion, established tumors may actually depend on elevated oxidative stress for their growth signaling. High-dose antioxidant supplements during active cancer treatment may reduce the oxidative damage that chemotherapy and radiotherapy use to kill cancer cells — potentially protecting the tumor as well as the patient. Advise patients receiving cancer treatment to discuss antioxidant supplement use with their oncologist before starting.

Type 2 Diabetes — The Bidirectional Relationship

In type 2 diabetes, oxidative stress and hyperglycaemia form a vicious cycle — each worsening the other. Understanding this cycle explains why glycaemic control alone is insufficient to prevent diabetic complications, and why dietary antioxidant protection has independent value in diabetes management.

Direction of Damage	Mechanism	Clinical Consequence
Hyperglycaemia → Oxidative stress	Excess glucose undergoes autooxidation; activates the polyol pathway (which depletes the antioxidant NADPH needed to regenerate glutathione); stimulates PKC which activates NADPH oxidase to produce superoxide	This is why diabetic complications develop even in patients whose cholesterol and blood pressure are well-controlled — the high glucose environment continuously generates free radicals that damage small vessels, nerves, and kidneys through mechanisms independent of lipid or pressure pathways.
Oxidative stress → Insulin resistance	Hydrogen peroxide and toxic fat aldehyde (4-HNE) impair the insulin signaling pathway at a specific point — blocking GLUT4 (the glucose transporter) from moving to the cell surface → cells cannot take up glucose properly	This creates the vicious cycle: insulin resistance → higher blood glucose → more free radicals → more insulin resistance. Dietary patterns that reduce oxidative stress (Mediterranean, DASH) improve insulin sensitivity through this mechanism, independently of weight loss.
Pancreatic beta-cell vulnerability	Beta cells have unusually low levels of antioxidant enzymes (catalase and GPx) compared to other tissues — making them particularly susceptible to hydrogen peroxide damage → beta cell death → progressive loss of insulin secretion	The progressive nature of beta cell loss in T2DM is partly an oxidative damage story. Dietary antioxidant protection of beta cells is a genuine preventive mechanism — particularly relevant in the pre-diabetes stage where beta cell rescue is still possible.

CONTEXT

In Sudan and Sub-Saharan Africa, T2DM prevalence is rising rapidly amid a dietary transition toward refined grains, ultra-processed foods, and reduced vegetable diversity — all of which increase oxidative burden while reducing dietary antioxidant supply. The mechanistic connections described here provide a biological rationale for dietary pattern intervention in T2DM prevention — not just caloric restriction, but specifically increasing dietary antioxidant density.

PART FIVE — Why Antioxidant Supplements Fail While Dietary Patterns Succeed

One of the most important and counterintuitive findings in clinical nutrition is that antioxidant supplements have largely failed — and in some cases caused harm — in large randomized controlled trials, while dietary patterns rich in the same antioxidants consistently protect health. Understanding why this happens is essential for evidence-based practice.

The Supplement Paradox

Why Food Works and Pills Often Don't

The Evidence from Clinical Trials

Trial	What Was Tested	What Happened	The Lesson
ATBC Trial (Finland, 1994)	Beta-carotene + vitamin E supplements in male smokers	Beta-carotene arm: 18% INCREASE in lung cancer. Trial stopped early.	Beta-carotene at high doses in a high-oxygen environment (smokers' lungs) behaves as a pro-oxidant, not an antioxidant. Context matters — the same molecule behaves differently at pharmacological vs. physiological doses.
CARET Trial (USA, 1996)	Beta-carotene + vitamin A in smokers and asbestos workers	28% increase in lung cancer; 17% increase in CVD mortality. Stopped 21 months early.	Amplified the ATBC finding — high-dose supplemental beta-carotene is harmful in smokers. Dietary beta-carotene from vegetables is protective.
HOPE and HOPE-TOO	Vitamin E 400 IU/day in patients at high CVD risk	No cardiovascular benefit; HOPE-TOO extended follow-up: increased risk of heart failure	High-dose vitamin E may displace the body's other tocopherols, disrupting the balance of the vitamin E family. Also may interfere with redox signaling that the body needs.
SELECT Trial (2011)	Vitamin E and/or selenium for prostate cancer prevention	Vitamin E arm: 17% increase in prostate cancer (in selenium-adequate men)	In men with adequate selenium, extra selenium disrupted normal redox balance. Extra vitamin E had pro-proliferative effects in the prostate microenvironment at pharmacological doses.
AREDS2 (Age-Related Eye Disease)	Lutein 10mg + zeaxanthin 2mg for age-related macular degeneration	25% reduction in progression to advanced AMD — one of the few positive supplement trials	This works because lutein and zeaxanthin accumulate specifically in the retina where they are needed, and at doses comparable to what high dietary intake would provide. Mechanism is specific and the tissue-targeting is natural.

Why Supplements Fail — The Four Reasons

Reason	Explanation	Implication for Counselling
1. Antioxidant network disruption	Isolated high-dose supplements overwhelm one part of the network, depleting the cofactors needed to regenerate that antioxidant. High vitamin C generates pro-oxidant activity in the presence of free iron. High beta-carotene at high oxygen tension becomes pro-oxidant.	The network is self-balancing at physiological concentrations. Pharmacological doses of single components distort the balance in unpredictable ways. This is why 'more is not better' for antioxidants.
2. Free radicals as necessary signals	The body uses low-level free radical production as cellular signals — for example, the free radicals produced during exercise activate mitochondrial biogenesis and strengthen cardiovascular fitness. High-dose antioxidants blunt these adaptive signals.	High-dose antioxidant supplements may reduce the benefits of exercise by suppressing the oxidative signal that triggers adaptation. Research by Ristow et al. showed that high-dose vitamins C and E blunted insulin sensitivity improvements from exercise in humans.
3. Food matrix and synergy	Thousands of compounds in plant foods work together — polyphenols activate Nrf2, carotenoids quench singlet oxygen, vitamin C regenerates vitamin E, fibre feeds bacteria that produce antioxidant metabolites. This synergy cannot be replicated in a capsule.	No supplement can deliver the food matrix. A tomato contains lycopene, vitamin C, beta-carotene, polyphenols, potassium, and fibre in proportions that evolved together. The supplement contains only lycopene.
4. Bioavailability and microbiome transformation	Many of the most protective plant compounds (ellagitannins → urolithins; isoflavones → equol; lignans → enterolactone) are inactive until transformed by gut bacteria. Supplements deliver the parent compound, bypassing the microbiome transformation that creates the active form in whole food.	Protecting and cultivating the gut microbiome (through dietary fibre, fermented foods, dietary diversity) is as important as the antioxidant intake itself. Supplements cannot replicate microbiome-dependent activation.

PRACTICE

The counselling message is clear: the evidence supports dietary patterns, not antioxidant supplements, as the primary dietary strategy for oxidative stress protection. The specific exceptions (lutein/zeaxanthin for AMD in those at risk; NAC for confirmed GSH depletion; selenium only when deficient) are narrow, condition-specific, and dose-limited. For the general population, the recommendation is a diverse, plant-rich, minimally processed dietary pattern — and the mechanisms described in this lecture explain precisely why.

PART SIX — Practical Guidance: Reducing Oxidative Stress Through Diet and Lifestyle

Dietary Strategies That Reduce Oxidative Stress

Strategy	Mechanism	Practical Application
Maximize plant food diversity	Each plant food family activates different components of the Nrf2 system and covers different parts of the antioxidant network; colour variety reflects phytochemical variety	Aim for at least 5 different plant food types per day across at least 3 colour categories; include at least one cruciferous, one allium, and one dark leafy green source weekly
Priorities specific Nrf2-activating foods	Sulforaphane (broccoli, especially sprouts); quercetin (onions, kale); EGCG (green tea); allicin (crushed raw garlic); lycopene (cooked tomatoes with fat); curcumin with piperine	These foods do not merely scavenge free radicals — they switch on the cell's own antioxidant gene expression. Small amounts consistently are more effective than large amounts occasionally.
Optimize cooking methods	Heat destroys vitamin C, folate, and myrosinase (the broccoli enzyme that makes sulforaphane); but heat improves lycopene and beta-carotene bioavailability	Steam or microwave cruciferous vegetables; cook tomatoes with olive oil; eat leafy greens lightly dressed with acid (vitamin C) and fat; crush garlic and rest before cooking
Ensure mineral cofactor adequacy	Selenium (GPx), manganese (MnSOD), copper/zinc (CuZnSOD), and riboflavin (GR) are essential for enzymatic antioxidant defense	Assess dietary intake of these minerals particularly in vegetarians, the elderly, and food-insecure populations; targeted supplementation where deficiency is confirmed
Reduce dietary pro-oxidant load	Ultra-processed foods, oxidized cooking oils (high-heat repeat frying), processed meats, high sugar intake, and excess alcohol all increase the oxidative burden the defesce system must handle	Frame this as reducing the demand on the antioxidant defesce system — not just adding antioxidant foods, but also reducing pro-oxidant inputs

Lifestyle Factors — Beyond Diet

- **Smoking cessation:** The single largest modifiable source of oxidative stress. Even passive smoke exposure is a significant pro-oxidant load. No dietary intervention fully compensates for active smoking.
- **Moderate physical activity:** Low-to-moderate exercise increases the body's antioxidant enzyme expression through hormetic free radical signaling — making the antioxidant defesce system more robust over time. Sedentary behaviour is an oxidative risk factor.
- **Adequate sleep:** Sleep deprivation increases oxidative stress markers and reduces antioxidant enzyme activity. Seven to nine hours per night is associated with lower oxidative stress biomarkers.

- Chronic stress management: Sustained psychological stress activates the hypothalamic-pituitary-adrenal axis and pro-inflammatory pathways, continuously generating free radicals. Stress reduction is not merely a psychological intervention — it is a biological one.
- Air quality: Indoor cooking fires, vehicle exhaust, and industrial pollution are significant environmental sources of oxidative stress particularly relevant in Sudan and across Africa. Ventilation, clean cooking fuels, and air filters reduce this burden.

Clinical Scenario: Connecting the Lecture to a Real Patient

- Ahmed is a 56-year-old teacher. He has type 2 diabetes (HbA1c 8.4%), hypertension, and is a former smoker (stopped 5 years ago). He lives in Khartoum. His diet consists primarily of white rice and bread, sugary tea with every meal, some meat, minimal vegetables, and occasional fruit. He uses a cooking fire for his meals. He has heard that 'antioxidant supplements' are good for health and asks whether he should start taking vitamin E and beta-carotene capsules.
- Question 1: Using the mechanisms from this lecture, identify four specific factors in Ahmed's history and dietary pattern that are contributing to his oxidative stress burden. For each, explain the mechanism.
- Question 2: His HbA1c of 8.4% indicates poor glycaemic control. Explain how this worsens his oxidative stress — and how his oxidative stress likely worsens his insulin resistance. Draw the vicious cycle.
- Question 3: How would you respond to his question about vitamin E and beta-carotene supplements? What is the evidence, and what is your recommendation?
- Question 4: Design a specific, culturally appropriate, and practical dietary modification plan for Ahmed that addresses his oxidative stress burden using foods available in Sudan. Which foods would you prioritize and why?
- Question 5: Beyond diet, what lifestyle modifications would most meaningfully reduce his oxidative stress — and in what order of priority?

Critical Thinking Questions

- This lecture argues that free radicals are not simply harmful — the body uses them as signaling molecules, and the immune system uses them as weapons. High-dose antioxidant supplements may blunt both of these beneficial functions. How does this complexity change your approach to antioxidant supplement recommendations? Where is the line between supporting the antioxidant defense system and overwhelming it?
- The ATBC and CARET trials showed that beta-carotene supplements increased lung cancer in smokers — the opposite of the protective association seen with dietary beta-carotene. What does this tell us about the relationship between whole food nutrients and isolated supplements? What are the implications for how we communicate dietary antioxidant recommendations to patients who want 'something they can take'?

- Oxidative stress is a biological mechanism — but its drivers (smoking, ultra-processed food, air pollution, psychological stress, physical inactivity) are shaped by social, economic, and environmental conditions. How does understanding the oxidative stress mechanism change how you think about dietary counselling in populations facing food insecurity, environmental pollution, or high chronic stress?

Lecture Summary — Key Takeaways for Dietetic Practice

- Free radicals and ROS are produced continuously by normal metabolism (primarily mitochondria), immune activity, and environmental exposures (smoking, pollution, UV, processed food). They are unavoidable — but the rate of production and the capacity for defesce can be modulated by diet and lifestyle.
- The four major targets of oxidative damage: Fats (lipid peroxidation → oxidized LDL → atherosclerosis; measured by F2-isoprostanes, MDA); Proteins (carbonylation, nitration → enzyme inactivation, plaque formation); DNA (8-OHdG → mutations in oncogenes → cancer; measurable in urine); Glycation/AGEs (sugar-protein adducts → vascular stiffness, neuropathy, nephropathy, cataracts).
- The antioxidant defesce network: Enzymatic first line (SOD requires Mn, Cu, Zn; Catalase requires Fe; GPx requires Se; GR requires B2/riboflavin). Glutathione system (the master intracellular antioxidant; cysteine is rate-limiting; NAC is the clinical pro-drug). Nrf2 pathway (the master switch — activated by sulforaphane, quercetin, EGCG, curcumin, allicin → switches on 200+ protective genes). Dietary antioxidants (Vitamin E in membranes; Vitamin C in water phase; Carotenoids for singlet oxygen; Polyphenols via Nrf2 and direct scavenging — all working as a regenerating network).
- Disease connections: CVD (superoxide destroys NO → endothelial dysfunction; oxLDL → foam cells → plaque; NF-kB → inflammation → plaque rupture). Cancer (8-OHdG → mutations; NF-kB → clonal expansion; caution: high-dose antioxidants during treatment may protect tumour). T2DM (hyperglycaemia → ROS via polyol/PKC/mitochondrial pathways; ROS → insulin resistance via IRS-1 serine phosphorylation; beta-cell vulnerability due to low catalase/GPx).
- The supplement paradox: Large RCTs of antioxidant supplements (ATBC, CARET, HOPE, SELECT) have been neutral or harmful. Reasons: dose-dependent pro-oxidant activity; disruption of redox signaling needed for exercise adaptation; inability to replicate food matrix synergy; bypass of microbiome transformation. Exception: lutein/zeaxanthin for AMD (tissue-specific, physiological doses). Recommendation: dietary patterns over supplements for the general population.
- Practical guidance: Maximize plant food diversity and colour; prioritize Nrf2-activating foods (broccoli/sprouts, onions, green tea, garlic, tomatoes, turmeric with black pepper); optimize cooking methods (steam cruciferous, cook tomatoes with oil, rest crushed garlic before heat); ensure mineral cofactor adequacy (Se, Mn, Cu, Zn, B2); reduce pro-oxidant load (UPF, oxidized oils, alcohol, smoking, chronic stress, sedentary behaviour).

Suggested reading:

1. Halliwell B & Gutteridge JMC (2015). Free Radicals in Biology and Medicine, 5th Ed. — the definitive reference. |
2. Sies H, Berndt C & Jones DP (2017). Oxidative Stress. Annual Review of Biochemistry. |
3. Ristow M et al. (2009). Antioxidants prevent health-promoting effects of physical exercise in humans. PNAS. |
4. Steinhubl SR (2008). Why have antioxidants failed in clinical trials? American Journal of Cardiology. |
5. PREDIMED Study Investigators (2013). Primary prevention of cardiovascular disease with a Mediterranean diet. NEJM.

Module 4 — Oxidative Stress, Phytochemicals & Functional Foods

A 3-Lecture Graduate Series: Free Radicals & Antioxidants • Phytochemicals • Fruits & Vegetables

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Phytochemicals: Sources & Benefits

Classification, Bioavailability, Mechanisms of Action & Chronic Disease Evidence

- ▶ Part 1: How Phytochemicals Work — Nrf2, NF-κB, AMPK & Gut Microbiome
- ▶ Part 2: The Major Phytochemical Families — Flavonoids | Phenolic Acids | Lignans | Glucosinolates | Allium | Carotenoids | Phytosterols | Curcumin | Berberine
- ▶ Part 3: Bioavailability — The Four Determinants & the Microbiome as Transformer
- ▶ Part 4: The Evidence Hierarchy — Strong | Moderate | Preliminary | Insufficient
- ▶ Clinical Case: Fatima — Nurse, Pre-Diabetes, Hypercholesterolaemia & Phytochemical Strategy

Phytochemicals

A Clinical Reasoning Approach: Food Sources, Mechanisms of Protection & Evidence-Based Health Benefits

Focus: Why specific plant foods protect health — and how to translate that into practical dietary recommendations

What Are Phytochemicals — and Why Do They Matter?

Phytochemicals are biologically active compounds found exclusively in plants. They are not vitamins or minerals — the body does not require them to prevent a classical deficiency disease. But they are far from nutritionally neutral. Decades of research consistently show that populations eating diverse, plant-rich diets have substantially lower rates of cardiovascular disease, several cancers, type 2 diabetes, and neurodegenerative disease — and that these protective effects cannot be fully explained by the vitamins, minerals, and fibre in those plants alone. The protection that remains after accounting for classical nutrients is largely attributable to phytochemicals.

WHY?

Plants produce phytochemicals for their own purposes — as pigments to attract pollinators, as bitter compounds to deter herbivores, as antimicrobials to prevent infection, and as UV screens to prevent radiation damage. When humans eat these plants, many of these defense and signalling compounds activate protective pathways in human cells that overlap with our own needs for disease prevention. This is why 'eat the rainbow' is not just a slogan — different plant colours reflect different phytochemical families with different protective mechanisms.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain what phytochemicals are, how they differ from classical nutrients, and why they are essential to a complete understanding of food and health
- Identify the major families of phytochemicals, their primary food sources, and the factors that affect how much the body can absorb and use
- Describe the key mechanisms by which phytochemicals protect health — focusing on the pathways relevant to cardiovascular disease, cancer, and type 2 diabetes
- Explain the role of the gut microbiome in transforming phytochemicals and why individual response to plant foods varies
- Distinguish between the strength of evidence for different phytochemicals — from strong epidemiological and trial evidence to promising but preliminary findings
- Translate phytochemical science into practical, culturally relevant dietary counselling recommendations

PART ONE — How Phytochemicals Work: The Four Key Mechanisms

Before examining individual phytochemical families, it is essential to understand how they protect health. Most phytochemicals do not work through a single mechanism — they activate multiple, overlapping pathways simultaneously. Four mechanisms are most clinically important and appear repeatedly across different phytochemical families.

Mechanism	What It Means in Plain Terms	Which Diseases It Protects Against	Example Phytochemicals
Activating the Nrf2 pathway (the cell's own defence gene switch)	Nrf2 is a master switch inside cells that, when activated, turns on over 200 genes — producing antioxidant enzymes, detoxification proteins, and anti-inflammatory molecules. Phytochemicals activate this switch, making the cell more resistant to oxidative damage and carcinogens.	Cancer prevention (Phase II detoxification enzymes neutralize carcinogens before they damage DNA); cardiovascular protection (endothelial defense); reduces oxidative stress in diabetes	Sulforaphane (broccoli sprouts — most potent known activator), curcumin, quercetin, EGCG (green tea), allicin (garlic), lycopene
Suppressing NF-kB (the inflammation gene switch)	NF-kB is the master switch for inflammation — when chronically activated, it produces a continuous stream of inflammatory molecules that damage blood vessels, promote cancer growth, and worsen insulin resistance. Many phytochemicals block this switch, reducing chronic low-grade inflammation.	Cardiovascular disease (arterial inflammation is central to atherosclerosis); cancer promotion (NF-kB keeps damaged cells alive); T2DM (inflammatory cytokines worsen insulin resistance); arthritis, IBD	Curcumin, quercetin, resveratrol, EGCG, anthocyanins, allicin, omega-3 fatty acids
Activating AMPK (the cellular energy sensor)	AMPK is a molecular sensor that detects when cells need more energy. When activated, it switches the cell into 'energy conservation mode' — improving glucose uptake, reducing fat synthesis, improving mitochondrial function, and mimicking some effects of caloric restriction and exercise.	Type 2 diabetes prevention and management (improves insulin sensitivity); cardiovascular disease (reduces lipid synthesis); obesity (reduces fat accumulation); cancer (AMPK activation suppresses mTOR, which cancer cells need for growth)	Berberine (most potent AMPK activator among phytochemicals; comparable to metformin), resveratrol, EGCG, quercetin, chlorogenic acid (coffee)
Gut microbiome transformation (the hidden converter)	Many phytochemicals cannot be absorbed in the small intestine — they arrive in the colon intact, where gut bacteria convert them into smaller, more bioavailable, and often more potent bioactive compounds. The individual's microbiome composition determines how effectively this conversion occurs.	All conditions benefited by phytochemicals — but the magnitude of benefit varies between individuals based on microbiome composition	Ellagitannins (pomegranate, walnuts) → urolithins; isoflavones (soy) → equol; lignans (flaxseed) → enterolactone; chlorogenic acid (coffee) → dihydrocaffeic acid

CONNECT

These four mechanisms explain a pattern that appears throughout this lecture: phytochemicals that activate Nrf2 tend to also suppress NF-kB (because Nrf2 activation produces molecules that block NF-kB); phytochemicals that activate AMPK tend to also reduce oxidative stress (because AMPK improves mitochondrial efficiency). This is why plant foods with diverse phytochemical content are more protective than any single isolated compound — multiple pathways are activated simultaneously.

PART TWO — The Major Phytochemical Families

Phytochemicals are classified by their chemical structure into several major families. Each family has characteristic food sources, bioavailability characteristics, and health effects. The most clinically important are covered in order of evidence strength.

Polyphenols — The Largest and Most Studied Family

Flavonoids, Phenolic Acids, Stilbenes & Lignans

The Flavonoid Sub-Family — Found in Almost Every Plant Food

Flavonoids are the most abundant polyphenols in the human diet — present in virtually all fruits, vegetables, legumes, tea, coffee, wine, and cocoa. They share a basic chemical structure but divide into six sub-classes with distinct food sources and health effects.

Flavonoid Sub-class	Primary Food Sources	Key Health Effect	Strength of Evidence
Flavonols (Quercetin, Kaempferol)	Onions (especially outer rings and red varieties), kale, broccoli, apples (skin), capers, tea, red wine	Blood pressure reduction; anti-inflammatory (NF-kB suppression); anti-atherosclerotic; inhibits carcinogen-activating enzymes (CYP1A1); chelates free iron (preventing Fenton reaction)	Strong — meta-analysis of >30 RCTs: quercetin significantly reduces systolic (-3.1 mmHg) and diastolic (-2.2 mmHg) BP, reduces CRP. Dietary quercetin inversely associated with CVD mortality in large cohorts (EPIC, Nurses' Health Study).
Flavan-3-ols (Catechins, EGCG)	Green tea (richest source: 50-300mg EGCG/cup), dark chocolate/cocoa (epicatechin), red wine, apples, grapes	Endothelial function improvement; blood pressure reduction; LDL-C reduction; neuroprotection; anti-cancer (epigenetic mechanisms — inhibits DNMT, reactivating silenced tumour-suppressor genes)	Strong — COSMOS trial: cocoa flavanol 600mg/day → 21% reduction in CVD mortality over 3.6 years. Meta-analyses: green tea → ~28% reduction in T2DM incidence; improved FMD (endothelial function marker) in 22 RCTs.

Anthocyanins (Cyanidin, Malvidin)	Blueberries, blackberries, raspberries, cherries, elderberries, red/purple grapes, red cabbage, purple corn	Endothelial protection; blood pressure reduction; improved insulin sensitivity; anti-inflammatory; neuroprotective; cross blood-brain barrier	Strong for CVD — blueberry RCTs: 1 cup/day for 6 weeks significantly improves flow-mediated dilation in metabolic syndrome. Anthocyanin intake inversely associated with T2DM risk (RR 0.85) in prospective cohorts. Elderberry meta-analysis: ~2 day reduction in cold/flu duration.
Flavanones (Hesperidin, Naringenin)	Citrus fruits — oranges (hesperidin), grapefruit (naringenin, naringin); concentrated in peel/pith, partially lost in juicing	Anti-inflammatory; improves lipid profile; grapefruit naringenin inhibits CYP3A4 in the intestine (significant drug interactions)	Moderate — RCTs show improvement in lipid profiles and inflammatory markers. Critically important for drug interactions: grapefruit juice inhibits CYP3A4 irreversibly → markedly increases blood levels of statins, cyclosporine, amlodipine, midazolam — interaction persists 24-72 hours after consumption.
Isoflavones (Genistein, Daidzein)	Soybeans, edamame, tofu, tempeh (highest bioavailability from fermented forms), miso, soy milk	Weak oestrogen-like activity (SERM) — beneficial for menopausal symptoms; protective against hormone-sensitive cancers in populations with lifelong exposure; modulated by gut microbiome (equol production)	Moderate/context-dependent — Asian cohort studies show inverse association with breast and prostate cancer; Western supplementation data mixed. ~25% reduction in hot flush frequency in RCTs. Safe for breast cancer survivors at food levels (WHO, WCRF consensus).
Stilbenes (Resveratrol)	Red grape skins, red wine (small amounts), peanuts, mulberries, Japanese knotweed (supplement source)	SIRT1 activation → mimics effects of caloric restriction; anti-inflammatory (NF-κB); cardioprotective in laboratory and some human studies	Mixed — compelling mechanistic data, limited clinical translation due to rapid metabolism (half-life <30 min). Some RCT benefit in T2DM and NAFLD; cardiovascular outcome trials neutral. Bioavailability-enhanced forms under development.

CAUTION

Grapefruit-drug interaction: This is a genuine, clinically significant safety issue that dietitians must know. Furanocoumarins in grapefruit (not naringenin itself) irreversibly inhibit intestinal CYP3A4, markedly increasing the bioavailability of CYP3A4-metabolised drugs. The interaction lasts 24-72 hours. Affected drugs include: simvastatin/atorvastatin (statin toxicity risk), cyclosporine (transplant rejection risk if dose appears too low), amlodipine, midazolam, tacrolimus. One glass of grapefruit juice can cause a clinically significant drug interaction.

Phenolic Acids — The Most Abundant Polyphenols in Most Diets

While flavonoids receive the most research attention, phenolic acids — particularly chlorogenic acids from coffee — are actually the most consumed polyphenols in Western and many African diets. A regular coffee drinker may consume over 1 gram of chlorogenic acid per day — more than any other single phytochemical category.

Phenolic Acid Source	Key Compounds	Primary Mechanisms	Clinical Evidence
Coffee (by far the largest source)	Chlorogenic acids (CQAs) — 70-350mg per cup; also diterpenes (cafestol, kahweol) in unfiltered coffee	Inhibits alpha-glucosidase and alpha-amylase (reduces postprandial glucose); inhibits hepatic glucose-6-phosphatase (reduces fasting glucose output); activates AMPK; Nrf2 activation; gut microbiome modulation	Meta-analysis (28 cohort studies, >1 million participants): 3-4 cups/day → 25-30% reduction in T2DM risk. Both caffeinated and decaffeinated coffee are protective — implicating chlorogenic acids, not caffeine. EPIC cohort: ~15% reduction in all-cause mortality with moderate coffee intake. Inverse associations with Parkinson's disease, Alzheimer's, liver cirrhosis, and hepatocellular carcinoma.
Whole grains, especially oats and rye	Ferulic acid (bound to cell walls; partially released by gut bacteria); avenanthramides (oats only)	Ferulic acid: antioxidant, anti-inflammatory, anti-cancer (inhibits carcinogen-activating CYPs); avenanthramides: anti-inflammatory, anti-itch, unique to oats	Dietary whole grain intake inversely associated with T2DM, CVD, and colorectal cancer across major cohort studies. Ferulic acid bioavailability from whole grains is low but enhanced by fermentation and cooking.
Berries, stone fruits	Ellagic acid, protocatechuic acid	Ellagic acid: precursor to ellagitannins which gut bacteria convert to urolithins — more bioactive than ellagic acid itself	Strawberries, raspberries, pomegranates — ellagic acid content high; but the key bioactive compounds are the urolithins formed in the colon. Individual variation is enormous (see gut microbiome section).

CONTEXT

Coffee is the world's most widely consumed phytochemical-rich beverage — including in Sudan, where it is deeply embedded in cultural practice (the jabana coffee ceremony, qahwa). The evidence consistently showing protective effects of moderate coffee consumption (3-4 cups/day) against diabetes, liver disease, and neurodegenerative disease is one of the most robust findings in nutritional epidemiology. For patients who already drink coffee, this is a dietary pattern to reinforce — not restrict.

Lignans — The Fermented-Food Phytochemicals

Lignans are phytochemicals found primarily in seeds and whole grains that require gut bacterial transformation to become biologically active. The parent compounds in food (secoisolariciresinol in flaxseed) are converted by specific gut bacteria into enterolactone and enterodiol — the active mammalian lignans with weak oestrogenic and anti-cancer activity.

Lignan Source	Amount	Health Effect	Key Point
Flaxseeds (richest source by far)	~300mg SDG per 100g — orders of magnitude more than other foods	Breast cancer risk reduction (postmenopausal); improved lipid profile; blood glucose control; antioxidant	Ground flaxseed is needed — whole seeds pass undigested. One tablespoon ground flaxseed daily provides meaningful lignan exposure. Also provides ALA (plant omega-3) and soluble fibre — a triple benefit.
Sesame seeds	High in sesamin and sesamolin — different lignan sub-types	Blood pressure reduction; antioxidant; anti-inflammatory	Sesame and sesame oil are widely used in Sudanese and Middle Eastern cooking — a culturally relevant lignan source. Sesame lignans have demonstrated antihypertensive effects in RCTs.
Whole grains (rye, barley, oats)	Lower amounts but consistently present	Contributes to total lignan intake in whole grain-eating populations	The shift from whole grain to refined grain in dietary transitions removes this lignan source — one of many micronutrient losses associated with food processing.

CONNECT

*The lignan story perfectly illustrates the microbiome-dependence of phytochemical action. Enterolactone production from flaxseed lignans requires specific bacteria (*Lactobifactor longoviformis*, *Blautia producta*). People with low microbiome diversity — from antibiotic overuse, low dietary fibre, or ultra-processed food-dominant diets — produce far less enterolactone from the same amount of flaxseed. This is why dietary fibre and fermented food intake are not separate from phytochemical benefit — they are prerequisites for it.*

Glucosinolates & Isothiocyanates

The Cruciferous Vegetable Compounds — Broccoli, Cabbage & Watercress

The Mechanism: Plant Defense as Human Medicine

Glucosinolates are sulphur-containing compounds produced by all cruciferous vegetables as a defense against insects — they taste bitter and are toxic to many pests. When cruciferous

vegetables are cut, chewed, or damaged, an enzyme called myrosinase (stored separately in the plant) contacts the glucosinolates and converts them into isothiocyanates (ITCs) — the biologically active compounds. In humans, these ITCs are among the most potent known activators of Nrf2 and the body's detoxification system.

WHY?

The myrosinase-glucosinolate system is the plant equivalent of a binary chemical weapon — harmless when the plant is intact, activated only when the plant is damaged. For humans eating cruciferous vegetables, the practical implication is critical: myrosinase is heat-sensitive. Boiling cruciferous vegetables for extended periods destroys myrosinase and dramatically reduces ITC formation. How you cook the vegetable determines how much of the cancer-protective compound you actually receive.

Cruciferous Vegetable Family	Key Glucosinolate / ITC Produced	Primary Protective Mechanism	Cooking Guidance
Broccoli, especially broccoli sprouts (sprouts contain 10-100x more)	Glucoraphanin → Sulforaphane (SFN) Most studied and most potent dietary Nrf2 activator known	SFN modifies Keap1 (the Nrf2 'keeper') → Nrf2 switches on Phase II detoxification enzymes (GST, NQO1, HO-1, GCL) → carcinogens neutralized before DNA damage; also inhibits HDAC (reactivates silenced tumour-suppressor genes); anti-H. pylori activity; reduces hepatic glucose production in T2DM	Raw or lightly steamed. If cooking, add raw mustard seed powder or daikon radish (external myrosinase source) to cooked broccoli. Broccoli sprouts (30-50g) used in clinical trials — the most potent dietary source.
All cruciferous vegetables (cabbage, Brussels sprouts, kale, cauliflower)	Glucobrassicin → Indole-3-carbinol (I3C) → DIM (diindolylmethane) in the stomach	Modifies oestrogen metabolism — shifts toward less active oestrogen forms (2-OH vs 16alpha-OH); weak oestrogen receptor antagonist; inhibits CDK2/4 (cell cycle arrest); anti-angiogenic	Standard cooking is acceptable — indoles are heat-stable (unlike glucoraphanin). Include multiple cruciferous types weekly for ITC diversity.
Watercress, garden cress, radish	Gluconasturtiin → PEITC (phenethyl isothiocyanate)	Inhibits CYP2E1 and CYP2A6 — the liver enzymes that activate tobacco carcinogens into DNA-damaging forms; Phase 2 clinical trial demonstrated single watercress meal significantly reduced tobacco carcinogen metabolites in smokers	Best consumed raw — classic watercress salad is optimal delivery. One of the few phytochemicals with demonstrated carcinogen-blocking activity in human clinical trials.
Mustard seeds, horseradish, wasabi	Sinigrin → Allyl isothiocyanate (AITC)	Antimicrobial (including against food-borne pathogens); anti-cancer cell migration and invasion; activates TRPA1 receptor (the 'heat' sensation of wasabi/mustard)	Traditional condiments that deliver bioactive ITCs — culturally relevant in many cuisines where mustard is used in cooking and salad dressings.

EVIDENCE

Sulforaphane clinical evidence: Broccoli sprout extract reduced aflatoxin-DNA adducts (a marker of liver cancer risk) in a randomised trial in China. SFN (200 micromoles/day) reduced PSA velocity in men with recurrent prostate cancer. Broccoli sprout extract significantly reduced fasting blood glucose and HbA1c vs placebo over 12 weeks in T2DM patients. These are Phase II clinical trial results — not just laboratory data.

PRACTICE

The practical counselling message for cruciferous vegetables has two parts: (1) Include them regularly — at least 3-5 servings per week; the epidemiological evidence for cancer protection is consistent. (2) Prepare them to maximise ITC delivery — steam or microwave rather than boil; eat some raw; add mustard to cooked broccoli. A patient who eats boiled Brussels sprouts every day may receive far less sulforaphane than one who eats raw broccoli florets twice per week.

Organosulfur Compounds from Allium Vegetables

Garlic, Onions, Leeks — The Cardiovascular Phytochemicals

The Allicin System — Another Binary Mechanism

Like glucosinolates in cruciferous vegetables, the bioactive compounds in allium vegetables are formed only when the plant is damaged. In garlic, alliin (an inactive sulphur-containing amino acid) contacts alliinase (the activating enzyme) when the clove is cut or crushed — producing allicin, the compound responsible for garlic's characteristic odour and most of its biological activity. Allicin is unstable and rapidly transforms into other active sulphur compounds (diallyl disulphide, diallyl trisulphide, ajoene) that are absorbed and active in the body.

Allium Vegetable	Key Phytochemicals	Primary Health Effects	Preparation Note
Garlic	Allicin (from crushing/chopping); DATS (diallyl trisulphide — most potent cancer-cell apoptosis inducer among garlic compounds); S-allylcysteine (SAC — the stable, most bioavailable compound in aged garlic extract)	CVD: reduces LDL-C, total cholesterol, triglycerides, and blood pressure (39-RCT meta-analysis); antimicrobial including <i>H. pylori</i> ; immune modulation; anti-cancer (HDAC inhibition, apoptosis induction); Nrf2 activation	Crush or mince and allow 10-minute rest before cooking — this maximizes allicin formation before heat destroys alliinase. Aged garlic extract (AGE/Kyolic) provides standardized, stable SAC — the preferred supplemental form.
Onions	Quercetin (highest concentration in outer rings and red/yellow varieties); fructooligosaccharides (FOS — prebiotic fibre); organosulfur compounds (less than garlic)	CVD protection (quercetin + organosulfur synergy); prebiotic effect (FOS → feeds <i>Bifidobacterium</i>); anti-platelet aggregation; anti-inflammatory	Quercetin is largely in the outer layers — avoid peeling too deeply. Red onions provide anthocyanins in addition to quercetin. Raw onions deliver more quercetin than cooked.
Leeks	Kaempferol (flavonol with anti-cancer properties in	Anti-cancer (kaempferol inversely associated with	Mild enough to use raw in salads —

	epidemiological studies); folate (64mcg/100g); vitamin K	ovarian and lung cancer in cohort studies); folate contribution; vitamin K for coagulation and bone health	reduces cooking-related phytochemical loss. Both the white bulb and green tops are nutritious.
Spring onions / Scallions	Quercetin, organosulfur compounds; vitamin K, vitamin C	Similar profile to onions with the added benefit of vitamin C and K from the green tops	The green tops should be included — they contain most of the vitamin K and additional polyphenols that are discarded if only the white part is used.

EVIDENCE	<i>Garlic supplementation meta-analysis (39 RCTs, n>2,600): significant reductions in total cholesterol (-17 mg/dL), LDL-C (-9 mg/dL), triglycerides (-11 mg/dL), and systolic blood pressure (-3.75 mmHg). Aged garlic extract (AGE) shows the most consistent cardiovascular evidence — standardised, odour-free, and bioavailable. Effect on blood pressure comparable to low-dose antihypertensive medication in mildly hypertensive individuals.</i>
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CONTEXT	<i>Garlic and onion are central to Sudanese cuisine — present in virtually every savoury dish. This is a case where culturally embedded traditional dietary patterns are delivering measurable health benefits that science is only now quantifying. The counselling message is reinforcement: the way Sudanese cooking uses abundant garlic and onion as flavour bases is nutritionally protective. Discouraging their use in the name of 'modern healthy eating' would be counterproductive.</i>
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Carotenoids Beyond Provitamin A

Lycopene, Lutein, Zeaxanthin & Astaxanthin

What Makes Non-Provitamin A Carotenoids Different

Beta-carotene's role as a vitamin A precursor was covered in the fat-soluble vitamins lecture. The non-provitamin A carotenoids discussed here do not convert to vitamin A — their health roles are entirely independent, based on their antioxidant properties (especially singlet oxygen quenching) and their selective accumulation in specific tissues where protection is most needed.

Carotenoid	Primary Food Sources	Where It Concentrates in the Body	Evidence-Based Health Role
Lycopene	Cooked and processed tomatoes (tomato paste, canned tomatoes, tomato sauce — more bioavailable than raw); watermelon; pink grapefruit; guava	Prostate gland, skin, liver, adrenal glands — particularly high concentration in prostate tissue	Prospective cohort evidence: highest lycopene quartile → ~40% reduction in prostate cancer risk (Health Professionals Follow-up Study); effect strongest for advanced and lethal disease. Phase 2

			RCT: lycopene 15mg/day reduced PSA, tumour proliferation index, and oxidative DNA damage pre-surgically. Cardioprotective — reduces LDL oxidation. Key point: cooking with fat dramatically increases bioavailability.
Lutein + Zeaxanthin	Kale (highest — 39mg/100g), spinach (12mg), collard greens, corn, egg yolk, orange peppers	Selectively accumulated in the retinal macula (the high-resolution central vision area) — the only carotenoids found there	AREDS2 RCT (gold standard evidence): lutein 10mg + zeaxanthin 2mg/day → 25% reduction in progression to advanced age-related macular degeneration (AMD). Replaced beta-carotene in the AREDS formula because beta-carotene increased lung cancer risk in smokers. Also accumulating in brain tissue — emerging cognitive data shows brain lutein correlates with processing speed and memory in older adults.
Astaxanthin	Wild salmon, krill, shrimp, microalgae (Haematococcus pluvialis — the commercial supplement source)	Cell membranes throughout the body; crosses the blood-brain barrier and blood-retinal barrier — penetrates tissues that most carotenoids cannot	10-100x more potent antioxidant than beta-carotene in laboratory measures. Reduces exercise-induced oxidative damage and inflammation in RCTs. Neuroprotective in preclinical models. Early trials in NAFLD and cognitive decline showing promise. Not currently a major dietary source for most populations — relevant primarily as a supplement consideration.
Beta-cryptoxanthin	Mandarins, tangerines, oranges, papayas, paprika, pumpkin	Lung tissue, joints	Both provitamin A activity (can convert to vitamin A) and independent antioxidant role. Inverse association with lung cancer (non-smoking-related mechanism), rheumatoid arthritis, and bone loss in prospective cohort studies. May have bone-protective effects independent of vitamin A.

WHY?

Lycopene's bioavailability story is the most important practical point in this section: raw tomatoes provide approximately 3mg lycopene per 100g with low bioavailability; tomato paste provides 45mg per 100g with much higher bioavailability because cooking breaks down cell walls and converts trans-lycopene to the more easily absorbed cis-isomer. Adding olive oil further increases absorption because lycopene is fat-soluble. A traditional Sudanese/Middle Eastern tomato-based sauce cooked in oil is actually a superior lycopene delivery vehicle to a raw tomato salad.

Phytosterols — The Cholesterol Competitors

Plant Compounds That Block Cholesterol Absorption

How Phytosterols Work

Phytosterols are structural components of plant cell membranes — the plant equivalent of cholesterol. Because their chemical structure is very similar to cholesterol, they compete with cholesterol for absorption in the intestine: when phytosterols are present, less cholesterol can be absorbed. This makes phytosterols unique among phytochemicals — they have a well-established, specifically approved health claim for LDL cholesterol reduction, supported by over 100 randomized controlled trials.

Phytosterol Source	Amount per Serving	Effective Dose for LDL Reduction	Clinical Evidence
Plant oils (wheat germ, sesame, corn, sunflower)	Significant amounts in unrefined oils; largely removed in refining	2g/day is the clinically effective dose — difficult to achieve from unfortified foods alone	Meta-analysis of >100 RCTs: 2g/day phytosterol esters → ~10% reduction in LDL-C. Effect is additive to statin therapy. FDA-approved health claim: 'Foods containing at least 0.65g of plant sterol esters per serving, eaten twice a day with meals, may reduce the risk of heart disease.' European Society of Cardiology: Class IIa recommendation.
Nuts (pistachios, almonds, walnuts)	~100-200mg per 30g serving	Would require 10+ servings of nuts to reach 2g — supplementary sources needed for therapeutic effect	Nuts provide phytosterols as part of a package with unsaturated fats, protein, fibre, and polyphenols — the combination likely more beneficial than phytosterols alone
Fortified foods (margarines, orange juice, yogurt)	Specifically formulated to deliver 1.0-1.5g per serving	2 servings daily achieves therapeutic dose reliably	Fortified margarines and dairy products are the primary clinical delivery vehicle. Note: high-dose phytosterols reduce carotenoid absorption — advise adequate carotenoid-rich food intake alongside phytosterol products.

PRACTICE

Phytosterols are the most evidence-based phytochemical intervention for LDL reduction — with a level of evidence comparable to low-dose statin therapy for mild hypercholesterolaemia. For patients with LDL above target who decline or cannot tolerate statins, phytosterol-enriched foods (2g/day) are a first-line dietary intervention with a Class IIa ESC recommendation. This is one area where supplementation (via fortified foods) has robust RCT evidence.

Curcumin, Berberine & Other High-Interest Phytochemicals

Strong Mechanisms, Variable Clinical Evidence

Curcumin — High Mechanism, Low Bioavailability

Curcumin is the primary active polyphenol in turmeric (*Curcuma longa*). It has been studied in over 120 completed clinical trials and has demonstrated potent anti-inflammatory, antioxidant, anti-cancer, and metabolic effects in laboratory and early clinical studies. Its major limitation is extremely poor oral bioavailability — rapidly metabolized and eliminated before reaching significant tissue concentrations.

Curcumin Mechanism	Clinical Application	Evidence Level
NF- κ B inhibitor (binds IKK-beta directly — one of the most potent natural NF- κ B inhibitors known)	Osteoarthritis: 1g/day curcumin comparable to NSAIDs (ibuprofen equivalent) for knee pain in RCTs	Moderate — consistent positive RCTs in OA; effect comparable to NSAIDs at standard doses
AMPK activator + PPARgamma agonist (insulin sensitising)	Pre-diabetes: T2DM conversion reduced by 78% vs placebo over 9 months (n=240 RCT). Reduces HOMA-IR in metabolic syndrome.	Moderate — notable pre-diabetes RCT; metabolic syndrome data consistent across multiple small RCTs
Nrf2 activator (inducible antioxidant enzyme expression)	NAFLD: improved liver enzyme levels (ALT), reduced liver steatosis in RCTs	Moderate — multiple RCTs in NAFLD; liver-specific benefits most consistent
HDAC inhibitor + direct anti-tumour effects in cell models	Cancer prevention: Phase 2 trials in colorectal cancer show colonocyte penetration; Phase 3 trials ongoing	Preliminary — compelling mechanistic data; Phase 3 trial results awaited

CAUTION

Standard turmeric in cooking delivers minimal pharmacological curcumin — estimated 2-5% absorption of a small amount. For therapeutic effects demonstrated in clinical trials, bioavailability-enhanced formulations are necessary: piperine (black pepper) increases curcumin half-life 20-fold (BioPerine); lipid-formulated (phospholipid complex, phytosome); or nanoparticle/liposomal preparations. Counsel patients: cooking with turmeric is beneficial for its modest anti-inflammatory effect, but clinical trial doses require standardised supplements.

Berberine — The Phytochemical Most Comparable to a Drug

Berberine is an alkaloid found in *Berberis* (barberry), *goldenseal*, and *Coptis* species. It is one of the most pharmacologically active phytochemicals known — activating AMPK through the same pathway as metformin (inhibiting mitochondrial Complex I → raising AMP:ATP ratio → AMPK activation) and inhibiting PCSK9 (the enzyme that degrades LDL receptors — the same target as the PCSK9 inhibitor drugs).

Berberine Effect	Mechanism	Clinical Evidence
Reduces fasting blood glucose and HbA1c	AMPK activation → improved GLUT4 expression and glucose uptake; reduces hepatic glucose output	Meta-analysis (14 RCTs): berberine comparable to metformin for FPG, HbA1c, and triglyceride reduction in T2DM patients. This is one of the strongest phytochemical-to-drug comparisons in the literature.
Reduces LDL cholesterol	Inhibits PCSK9 → increases LDL receptor recycling on hepatocytes → more LDL cleared from blood	Meta-analysis: berberine reduces LDL-C by ~25mg/dL — clinically meaningful, comparable to low-dose statins in mild hypercholesterolaemia
Gut microbiome modulation	Increases short-chain fatty acid-producing bacteria; reduces inflammatory dysbiosis	May explain part of its metabolic effect — a gut-mediated mechanism in addition to direct AMPK and PCSK9 effects
PCOS management	Improves insulin sensitivity and hormonal profile in PCOS	Several RCTs show berberine comparable to metformin in PCOS — with a potentially better lipid profile improvement

CAUTION

Berberine has genuine pharmacological potency — which means it also has genuine drug interaction potential. It inhibits CYP3A4 and P-glycoprotein, potentially increasing blood levels of many drugs including cyclosporine, some antibiotics, and anticoagulants. It should not be combined with metformin without medical supervision (additive hypoglycaemic effect). Unlike most phytochemicals where the concern is insufficient effect, berberine's concern is that it is effective enough to cause interactions. Treat it as a supplement with drug-like properties.

PART THREE — Bioavailability: Why the Same Food Affects People Differently

One of the most important and underappreciated aspects of phytochemical science is that the same food can deliver very different amounts of active phytochemicals to different people — depending on how the food was prepared, what was eaten with it, and critically, what bacteria live in the person's gut. This explains why clinical trials of phytochemicals show wide individual variation, and why blanket supplement recommendations for isolated compounds often fail.

The Four Bioavailability Determinants

Factor	How It Affects Phytochemical Delivery	Practical Implication
Food preparation and cooking method	Myrosinase (cruciferous vegetables) is heat-labile — boiling destroys it, preventing ITC formation. Lycopene (tomatoes) bioavailability is increased by cooking and fat co-ingestion. Quercetin is partially lost in boiling water. Allicin requires mechanical	The 'how you cook it' question is as important as 'what you eat' for phytochemical delivery. This is why food preparation education is an essential component of phytochemical-focused dietary counselling.

	damage (chopping/crushing) plus 10 minutes before cooking.	
Food matrix and fat co-ingestion	Carotenoids (lycopene, beta-carotene, lutein), curcumin, and other fat-soluble phytochemicals are absorbed dramatically better when consumed with fat (2-10x improvement). Low-fat dressings on salads substantially reduce carotenoid absorption.	Add olive oil, avocado, nuts, or seeds to salads and vegetable dishes — not just for their own nutritional value, but to enhance phytochemical absorption from the vegetables. This is another reason why low-fat plant-based diets may not maximize phytochemical bioavailability.
Gut microbiome — the primary transformer	Many phytochemicals are inactive until gut bacteria convert them to bioactive forms. Ellagitannins → urolithins (requires Gordonibacter and Ellagibacter species). Isoflavones → equol (requires Slackia isoflavoniconvertens — present in only ~30% of Western adults but ~60% of Asian adults). Lignans → enterolactone (requires Lactonifactor longoviformis).	Individual response to soy foods, pomegranate, and flaxseed depends on which bacteria the individual harbours. This explains population-level differences in phytochemical health effects and why the same RCT food intervention shows wide individual variation.
Phase II metabolism in the intestine and liver	Polyphenols are rapidly glucuronidated, sulfated, and methylated in intestinal cells and the liver — reducing their half-life in blood. Aglycone forms (without sugar) are generally more bioavailable than glycoside forms (with sugar). Piperine from black pepper inhibits glucuronidation, increasing many polyphenols' half-life.	The brief window of plasma polyphenol activity means consistent daily intake is more effective than occasional large doses. Fermented foods (where gut bacteria have already deglycosylated polyphenols before consumption) may provide more bioavailable forms.

The Gut Microbiome as Phytochemical Transformer

The relationship between dietary phytochemicals and the gut microbiome is bidirectional and clinically important. Phytochemicals modulate the microbiome (acting as prebiotics, selectively feeding beneficial bacteria). And the microbiome transforms phytochemicals into more potent bioactive compounds. Disrupting the microbiome through antibiotics, ultra-processed food, or low dietary fibre simultaneously reduces the phytochemical benefit of an otherwise good diet.

Phytochemical	What Gut Bacteria Do to It	Why This Matters
Ellagitannins (pomegranate, walnuts, raspberries, strawberries)	Gordonibacter and Ellagibacter species convert ellagitannins → urolithins A, B, C. Urolithin A activates mitophagy (cellular cleanup of damaged mitochondria) and mitochondrial biogenesis — effects not present in the parent ellagitannin.	~40% of people are 'urolithin producers' with the right bacteria; ~60% are non-producers or produce only less active forms. A person's response to pomegranate consumption depends entirely on their microbiome, not just their dietary intake. Clinical trials of Mitopure (purified urolithin A) bypass this by supplementing the bioactive compound directly.

Isoflavones — daidzein (from soy)	Slackia isoflavoniconvertens and Lactococcus sp. convert daidzein → equol. Equol is a more potent phytoestrogen than daidzein itself and is responsible for most of the hormonal and cancer-protective effects attributed to soy.	~30% of Western adults produce equol; ~50-60% of Asian adults (explaining why soy-cancer protection evidence is stronger in Asian than Western populations). Equol production can be enhanced by increasing dietary fibre and fermented food intake — cultivating the relevant bacteria.
Lignans from flaxseed and whole grains	Lactonifactor longoviformis and Blautia producta convert SDG (secoisolariciresinol diglucoside) → enterodiols → enterolactone	Enterolactone plasma levels inversely associated with breast cancer risk and cardiovascular mortality in prospective studies — but enterolactone production requires specific bacteria that may be absent or reduced in antibiotic users, people on low-fibre diets, or those with IBD.
Chlorogenic acids from coffee	Colonic bacteria convert chlorogenic acids into dihydrocaffeic acid and dihydroferulic acid — compounds that may be partly responsible for coffee's protective effects	Even when coffee polyphenols are poorly absorbed in the small intestine, their transformation products in the colon enter the circulation and reach tissues — extending the window of bioactivity well beyond the initial absorption phase.

PRACTICE	<i>The microbiome implication for dietary counselling: recommending phytochemical-rich foods is necessary but not sufficient if the patient's microbiome cannot transform them. Simultaneously: increase dietary fibre (feeds bacteria that transform phytochemicals); include fermented foods (adds relevant transforming bacteria); reduce antibiotic overuse; reduce ultra-processed food intake (which reduces microbiome diversity). Phytochemical recommendations and microbiome health recommendations are inseparable.</i>
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PART FOUR — The Evidence: What We Know, What We Think We Know, and What We Don't

A critical skill for clinical dietitians is the ability to accurately assess the strength of evidence for a phytochemical health claim — to distinguish between what has been demonstrated in randomized controlled trials versus what is supported only by epidemiological associations or laboratory data. The following framework classifies the major phytochemicals by evidence level.

Evidence Level	What It Means	Phytochemicals at This Level
STRONG — RCT evidence for clinical outcomes	Randomized controlled trials showing a meaningful effect on a clinically relevant endpoint (not just a biomarker)	Plant sterols: 2g/day → 10% LDL reduction (>100 RCTs). Lutein+zeaxanthin: 25% reduction in AMD progression (AREDS2). Cocoa flavanols: 21% reduction in CVD mortality (COSMOS). Garlic extract: reduces cholesterol and BP (39-RCT meta-analysis). Berberine: comparable to metformin for glucose and lipids (multiple RCTs).
MODERATE — Consistent	Strong consistent inverse associations in large cohort studies + mechanistic plausibility	Quercetin: BP reduction in meta-analysis of RCTs; CVD mortality associations in large cohorts. Sulforaphane: reduced carcinogen DNA adducts in

epidemiological + biomarker RCTs	+ RCT evidence on intermediate biomarkers (not final clinical outcomes)	human trial; preclinical cancer evidence strong. Lycopene: ~40% prostate cancer risk reduction in cohort data; Phase 2 trial data. Curcumin: OA pain, NAFLD, pre-diabetes RCTs positive. Chlorogenic acid (coffee): T2DM risk reduction in >28 cohort studies; decaffeinated coffee equally protective.
PRELIMINARY — Mechanistic + early phase trials	Compelling mechanisms in cell and animal models; Phase 1/2 clinical data; promising but not yet practice-changing	Resveratrol: strong mechanistic data (SIRT1, AMPK), limited clinical translation due to bioavailability. Urolithins: Phase 2 trial data on muscle function in elderly. Fisetin (strawberries): senolytic activity in early human trials. Berberine in PCOS: multiple positive RCTs but smaller studies. Astaxanthin: exercise performance RCTs positive; NAFLD early trial data.
INSUFFICIENT — Associations only or conflicting data	Interesting but not yet ready for clinical recommendation	Many specific phytochemicals in isolation. Resveratrol cardiovascular outcomes (neutral in RCTs despite mechanistic promise). Most specific carotenoid-cancer associations beyond lycopene-prostate. Isolated supplement interventions for cancer prevention in generally healthy populations.

CAUTION

A critical clinical warning: the categories above apply to whole food sources of phytochemicals unless specifically noted as supplement evidence. In several cases (beta-carotene, vitamin E, selenium at excess doses), supplement trials showed harm while dietary intake remains protective. Never extrapolate positive evidence from food-based phytochemical research to isolated high-dose supplement recommendations without checking specifically for supplement trial data.

Clinical Scenario: Applying Phytochemical Knowledge in Practice

- Fatima is a 48-year-old nurse with a family history of breast cancer, pre-diabetes (FPG 108 mg/dL, HbA1c 6.1%), and mild hypercholesterolaemia (LDL 152 mg/dL). She is postmenopausal (natural menopause at 46), non-smoker, does not drink coffee ('I was told it's bad for health'), and eats a diet that is moderate in vegetables but heavy in refined grains and processed foods. She has heard that 'antioxidant supplements' and 'soy isoflavones' are good for breast cancer prevention and asks your advice.
- Question 1: Which phytochemical-rich foods would have the strongest evidence base for reducing Fatima's three clinical concerns (breast cancer family history, pre-diabetes, hypercholesterolaemia)? Identify at least 6 specific foods and explain the mechanism for each.
- Question 2: She asks specifically about soy isoflavone supplements for breast cancer prevention. What does the evidence show — and is this safe for her? How does her postmenopausal status affect your recommendation?
- Question 3: She avoids coffee based on advice she received years ago. What would you tell her about the evidence on coffee and her specific health concerns?
- Question 4: She is enthusiastic about phytochemicals and wants to take a comprehensive 'antioxidant supplement' containing beta-carotene, vitamin E, and lycopene. What is your evidence-based response?

- Question 5: Fatima mentions she has been on antibiotics for a urinary tract infection for the past 3 weeks. How does this affect the phytochemical benefit she is receiving from her diet — and what would you recommend?

Critical Thinking Questions

- Berberine is described in this lecture as having clinical evidence comparable to metformin for glucose control in T2DM. If a patient with pre-diabetes asks whether they can use berberine instead of metformin, what is your role as a dietitian in this conversation? What factors would determine your response — and what would you advise?
- The gut microbiome section explains that approximately 40% of people cannot convert ellagitannins to urolithins, and only ~30% of Western adults produce equol from soy isoflavones. This means the same dietary recommendation will have very different effects in different patients. How does this individuality of phytochemical response challenge the way we currently provide dietary advice — and what practical tools are available to account for it?
- The lecture notes that garlic and onion are already central to Sudanese cuisine, and that coffee consumption is culturally widespread. How does understanding the phytochemical science of these foods change your approach to dietary counselling in Sudanese populations — and what other traditional foods from Sudan and East Africa might deserve attention from a phytochemical perspective?

Lecture Summary — Key Takeaways for Dietetic Practice

- Phytochemicals are biologically active plant compounds that are not essential nutrients but that contribute substantially to the health-protective effects of plant-rich diets. They work through four primary mechanisms: Nrf2 activation (switches on antioxidant and detoxification genes); NF-kB suppression (reduces chronic inflammation); AMPK activation (improves metabolic function); and gut microbiome transformation (converts inactive forms to potent bioactives).
- Major families and their strongest evidence: Flavonoids (quercetin → BP; cocoa flavanols → CVD mortality; anthocyanins → endothelial function and T2DM); Phenolic acids (chlorogenic acid from coffee → 25-30% T2DM reduction); Glucosinolates/sulforaphane (broccoli → Nrf2/cancer prevention, carcinogen blocking, glucose reduction in T2DM RCTs); Allium organosulfur compounds (garlic → LDL, cholesterol, BP reduction across 39 RCTs); Carotenoids (lutein/zeaxanthin → AMD prevention RCT evidence; lycopene → prostate cancer in cohort data); Phytosterols (2g/day → 10% LDL reduction — strongest phytochemical-LDL RCT evidence); Berberine (comparable to metformin in T2DM RCTs — treat as a pharmacologically active compound with drug interactions).
- Bioavailability is shaped by preparation (myrosinase destroyed by boiling — steam cruciferous vegetables; lycopene increased by cooking with fat; allicin requires crushing then 10 minutes rest before heat); fat co-ingestion (2-10x improvement for fat-soluble phytochemicals); gut microbiome (urolithins from ellagitannins, equol from isoflavones, enterolactone from lignans — all require specific gut bacteria); and phase II metabolism (rapid conjugation limits half-life; consistent daily intake is more effective than occasional large doses).
- Evidence hierarchy: STRONG (plant sterols, lutein/zeaxanthin for AMD, cocoa flavanols, garlic, berberine). MODERATE (quercetin, sulforaphane, lycopene, curcumin, coffee). PRELIMINARY (resveratrol, urolithins, fisetin, astaxanthin). Never extrapolate whole-food

evidence to high-dose isolated supplements without specifically checking supplement trial data — beta-carotene and vitamin E at supplement doses have caused harm.

- Grapefruit drug interaction: furanocoumarins irreversibly inhibit CYP3A4 for 24-72 hours — significantly increases blood levels of statins, cyclosporine, amlodipine, midazolam, and many other drugs. This is a clinical safety issue requiring patient education.
- Practical counselling principles: recommend dietary patterns over supplements; connect traditional/cultural food practices to phytochemical science (garlic, onion, turmeric, coffee in Sudanese/African contexts); teach preparation matters (steam vs boil, add fat to salads, crush garlic before cooking); support microbiome health (fibre, fermented foods) as a prerequisite for phytochemical benefit; assess evidence level before recommending any supplemental phytochemical.

Suggested reading:

1. Manach C et al. (2004). Polyphenols: food sources and bioavailability. *American Journal of Clinical Nutrition*. |
2. Rowland I et al. (2018). Gut microbiota composition in relation to the metabolic transformation of phytochemicals. *European Journal of Nutrition*. |
3. Dinkova-Kostova AT & Talalay P (2008). Direct and indirect antioxidant properties of inducers of cytoprotective proteins. *Molecular Nutrition & Food Research*. |
4. COSMOS Investigators (2022). Cocoa supplement and multivitamin outcomes study. *American Journal of Clinical Nutrition*. |
5. Vuorisalo T & Arjamaa O (Eds.). *Evolution of Obesity. Chapter on plant secondary metabolites and human health*.

Module 4 — Oxidative Stress, Phytochemicals & Functional Foods

A 3-Lecture Graduate Series: Free Radicals & Antioxidants • Phytochemicals • Fruits & Vegetables

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Fruits & Vegetables: Micronutrient Powerhouses

Nutritional Composition, Bioavailability, Public Health Evidence & Counselling Strategies

- ▶ Part 1: The Public Health Case — Global & Sudanese F&V Gap
- ▶ Part 2: Nutritional Profiles by Group — 8 F&V Groups with Sudanese Context
- ▶ Part 3: The Cooking Question — How Preparation Affects Nutrient Delivery
- ▶ Part 4: Disease Connections — CVD | Cancer | Type 2 Diabetes
- ▶ Part 5: Counselling in Practice — Barriers, Colour Framework & Special Populations
- ▶ Clinical Case: Nadia — Port Sudan, Hypertension, Pre-Diabetes & Postpartum Anaemia

Fruits & Vegetables

A Clinical Reasoning Approach: Why They Matter, What They Provide, How They Protect, and How to Counsel Effectively

Focus: Moving beyond food lists — understanding why F&V are irreplaceable and how to counsel diverse patient populations

Why Fruits and Vegetables? Building the Clinical Case

Fruits and vegetables (F&V) are not simply 'healthy foods' — they are the single most nutrient-dense food category per calorie available to humans, providing vitamins, minerals, dietary fibre, and thousands of phytochemicals in combinations that no supplement can replicate. Yet globally, insufficient F&V consumption is among the leading dietary contributors to preventable death, responsible for an estimated 7.8 million deaths per year. Understanding why this gap exists — and how to close it in practice — is one of the most important skills a clinical dietitian can develop.

WHY?

The question is not 'are F&V good for you?' — the evidence for that is overwhelming. The question is: Why specifically? What do they provide that other foods don't? How does that translate into protection against the diseases our patients have or are at risk for? And how do we counsel patients to actually eat more of them, given the real barriers they face? This lecture answers all four questions.

Learning Outcomes — By the end of this lecture, students will be able to:

- Explain why F&V are nutritionally irreplaceable and quantify the global and regional disease burden attributable to inadequate intake
- Profile the micronutrient and phytochemical composition of the major F&V groups, and explain the clinical significance of each key nutrient
- Explain how cooking method, storage, and food form (fresh, frozen, canned) affect micronutrient delivery — and translate this into practical preparation guidance
- Connect F&V intake to the specific mechanisms that protect against cardiovascular disease, cancer, and type 2 diabetes
- Identify the barriers to adequate F&V consumption and design evidence-based, culturally appropriate counselling strategies for diverse patient populations
- Apply the 'colour framework' and 'whole food over juice' principle to patient counselling across different clinical contexts

PART ONE — The Public Health Case: Why This Matters

Before examining individual nutrients and foods, it is important to understand the scale of the problem. Low F&V intake is not a minor dietary sub optimality — it is a leading cause of preventable chronic disease and death globally.

The Global F&V Gap	Key Data Points
Disease burden	WHO estimates ~5.2 million deaths/year from insufficient fruit intake and ~2.7 million from insufficient vegetable intake. Combined, low F&V intake is the 4th leading dietary risk factor for global mortality, behind high sodium, low whole grains, and low nuts/seeds.
Intake vs. recommendation	WHO recommends ≥400g F&V/day (5+ servings). >50% of the global population fails to meet this. In many low- and middle-income countries, average intake is under 200g/day. Even in high-income countries, only 10-30% of adults meet recommendations.
The dose-response relationship	Aune et al. (Lancet, 2017, n>2.5 million): Each additional 80g serving/day of F&V is associated with 8% lower CVD mortality, 6% lower cancer mortality, and 7% lower all-cause mortality. Benefit continues up to ~7-8 servings/day, with diminishing returns beyond that.
Sudan and Sub-Saharan Africa	Dietary transition toward refined grains, ultra-processed foods, and reduced vegetable diversity is occurring rapidly. Urban populations in Sudan, East Africa, and the Sahel are consuming fewer traditional plant foods (leafy greens, legumes, sorghum-based dishes) and more processed foods, creating a double burden: persistent micronutrient deficiency alongside emerging chronic disease.
Why supplements cannot substitute	F&V provide hundreds of compounds simultaneously — vitamins, minerals, phytochemicals, fibre, water, and anti-nutrient-reducing compounds — in ratios that evolved together. No supplement captures this. The ATBC, CARET, and Heart Protection Study trials showed that isolated antioxidant supplements from the same compounds fail to replicate the protection of whole food patterns.

CONTEXT

In Sudan and the wider East Africa/Sahel region, traditional dietary patterns included substantial vegetable diversity — wild leafy greens (karkade/hibiscus, mulukhiyah/molokhia, bamia/okra), legumes (ful medames, lentils), and allium-heavy cooking. These traditional foods are nutritionally exceptional. The dietary transition away from them is both a nutritional loss and a cultural disconnection. Counselling that reconnects patients with the nutritional value of traditional F&V is more culturally sustainable than introducing unfamiliar foods.

PART TWO — What Do F&V Actually Provide? Nutritional Profiles by Group

Different F&V groups provide very different nutrient profiles. A clinician who understands which groups provide which nutrients can make targeted recommendations based on a patient's specific deficiency risk or health condition — rather than offering a generic 'eat more vegetables' instruction that patients cannot act on.

Group 1 — Dark Leafy Green Vegetables

Spinach, Kale, Molokhia, Chard, Collards, Bok Choy, Arugula, Watercress

Dark leafy greens offer the highest micronutrient density per calorie of any food group. A single 100g serving of cooked spinach or kale delivers meaningful amounts of 8-10 different micronutrients simultaneously.

Nutrient	Best Leafy Green Sources (per 100g)	Why It Matters Clinically
Vitamin K1 (phyloquinone)	Swiss chard: 830µg; kale: 705µg; spinach: 483µg; collards: 623µg	Coagulation (factors II,VII,IX,X); osteocalcin carboxylation (bone mineralization); Matrix Gla Protein (MGP) activation — prevents arterial calcification. AI = 90-120µg/day. Warfarin interaction: counsel consistency, not avoidance.
Folate (B9)	Spinach: 194µg DFE/100g; asparagus: 149µg; romaine: 136µg	Neural tube defect prevention; DNA synthesis; one-carbon metabolism; homocysteine clearance. RDA = 400µg DFE (600µg in pregnancy). Heat-labile — raw or lightly cooked preserves more folate.
Lutein + Zeaxanthin	Kale: 39.5mg; spinach: 12.2mg; collards: 14.6mg; Swiss chard: 11mg	Macular pigment density (AMD and cataract prevention); blue light filtration in retina. AREDS2 RCT: 10mg lutein/day ↓25% slower AMD progression. No DRI established; ≥10mg/day studied clinically.
Magnesium	Spinach: 79mg; Swiss chard: 81mg; kale: 47mg	Cofactor for >300 enzymes; ATP synthesis; insulin receptor function; cardiovascular rhythm; muscle and nerve function. RDA = 310-420mg/day. Commonly low in diets high in processed food. Deficiency contributes to hypertension, T2DM, and muscle cramps.
Vitamin C	Kale: 93mg; watercress: 43mg; bok choy: 45mg	Aqueous-phase antioxidant; collagen synthesis (hydroxylation of proline/lysine); enhances non-haem iron absorption; RDA = 75-90mg/day. Destroyed by boiling — steam or eat raw to preserve.
Iron (non-haem)	Spinach: 2.7mg; Swiss chard: 1.8mg; kale: 1.5mg	Must be consumed with vitamin C to maximize absorption (reduces Fe ³⁺ to Fe ²⁺ for DMT1 uptake); phytate in spinach also reduces absorption. Combine with citrus, tomatoes, or peppers at the same meal.
Calcium	Bok choy: 105mg (bioavailability ~50%); kale: 150mg (bioavailability ~50%); spinach: 99mg (bioavailability ~5-8% due to oxalate)	Critical for bone health, nerve signaling, muscle contraction. The oxalate paradox: spinach calcium is poorly absorbed despite high content. Bok choy and kale calcium is better absorbed than dairy (32%). Critical for vegan/vegetarian counselling.
Beta-carotene (provitamin A)	Kale: 9.2mg; spinach: 5.6mg; Swiss chard: 3.6mg; molokhia: high	Converted to retinol (1 RAE per 12µg β-carotene from vegetables). Fat must be present for absorption. Critical in populations at risk for vitamin A deficiency.

CAUTION

The spinach calcium paradox is a critical clinical point: spinach is frequently recommended as a calcium source for vegans, but its oxalic acid content binds calcium in the gut and prevents absorption — the actual absorption rate is only 5-8%, compared to 50% from bok choy and ~32% from milk. A vegan patient eating spinach as their primary calcium source may be significantly calcium-deficient despite apparent adequate dietary intake. Always ask about specific sources, not just total calcium-containing foods.

CONTEXT

Molokhia (Corchorus olitorius — jute mallow) is a staple leafy green across Sudan, Egypt, and East Africa. It is exceptionally nutrient-dense: very high in beta-carotene, iron, calcium, magnesium, and B vitamins. It also contains mucilaginous polysaccharides with prebiotic properties. Nutritionally, it rivals any leafy green in the global literature — yet it appears in almost no Western nutrition textbook. Bamia (okra) similarly provides vitamin C, folate, magnesium, and soluble fibre (okra mucilage). These traditional Sudanese vegetables deserve scientific recognition.

Group 2 — Cruciferous Vegetables

Broccoli, Brussels Sprouts, Cauliflower, Cabbage, Kale, Bok Choy, Radish

Cruciferous vegetables are nutritionally exceptional on two levels: their conventional micronutrient content (vitamin C, K1, folate, calcium) and their glucosinolate/sulforaphane content covered in the Phytochemicals lecture. This dual benefit makes them among the most evidence-supported vegetables for chronic disease prevention.

Nutrient & Top Cruciferous Source	Amount	Clinical Significance
Vitamin C — Broccoli (89mg/100g raw); Brussels sprouts (85mg); cauliflower (48mg)	Exceeds orange in all three	~½ cup raw broccoli meets the entire adult RDA for vitamin C (75-90mg). Largely preserved by steaming; significantly lost by boiling. Superior to supplements because of food matrix co-factors.
Vitamin K1 — Kale (705µg); Brussels sprouts (177µg); broccoli (102µg)	1 serving provides 1-8x daily AI	Major dietary K1 source. For patients on warfarin: counsel consistent intake (not avoidance) — sudden large changes cause INR instability, but habitual intake allows stable dosing.
Folate — Broccoli (63µg/100g); Brussels sprouts (61µg); bok choy (66µg)	15-20% RDA per serving	Significant contributor to folate intake especially when consumed raw or lightly steamed. Particularly important for women of reproductive age.
Calcium — Bok choy (105mg; ~50% absorption); kale (150mg; ~50% absorption); broccoli (47mg; ~62% absorption)	High bioavailability	Cruciferous vegetables provide the most bioavailable non-dairy calcium available. Broccoli calcium absorption (~62%) actually exceeds dairy (~32%). Critical for vegans and lactose-intolerant patients.
Glucosinolates / Sulforaphane — Broccoli sprouts (highest); broccoli; Brussels sprouts; cabbage	Broccoli sprouts: ~1000mg glucoraphanin/100g	Nrf2 activation → Phase II detoxification enzyme induction → carcinogen neutralization. Epidemiology: 2-3 cruciferous servings/week ↓30% lower bladder and colorectal cancer risk. Maximised by raw or lightly steamed preparation; destroyed by boiling.

PRACTICE

The two most important preparation messages for cruciferous vegetables: (1) Steam or microwave rather than boil — boiling loses up to 50% of vitamin C and most of the glucosinolates that make cruciferous vegetables uniquely protective; steaming preserves both. (2) To maximize sulforaphane specifically — chop or chew the vegetable and allow a 10-minute rest before cooking. This lets the myrosinase enzyme act on glucoraphanin before heat destroys the enzyme. Adding raw mustard seed powder to cooked broccoli provides external myrosinase and restores sulforaphane production.

Group 3 — Orange & Yellow Vegetables

Sweet Potato, Carrots, Pumpkin, Butternut Squash, Orange Bell Pepper

Food (100g)	Standout Nutrients	Clinical Notes
Sweet potato (cooked)	Beta-carotene: 9.4mg; Vitamin C: 20mg; Potassium: 475mg; Manganese: 0.5mg; Fibre: 3g	One medium sweet potato provides ~100% daily vitamin A (as RAE). Higher GI than regular potato but higher micronutrient density. Skin provides additional fibre and polyphenols. Widely consumed in Sudan — an excellent counselling anchor.
Carrots (cooked)	Beta-carotene: 8.3mg; Potassium: 320mg; Vitamin K: 13µg	Cooking increases beta-carotene bioavailability by breaking cell walls. Fat co-ingestion essential — carrots with olive oil or butter provide dramatically more vitamin A than raw carrots alone. Purple carrots also contain anthocyanins.
Orange/yellow bell pepper (raw)	Vitamin C: 184mg (highest of any common vegetable); Vitamin B6: 0.3mg; Vitamin E: 1.6mg	Bell peppers provide more vitamin C per gram than any citrus fruit. Raw consumption preserves more vitamin C than cooking. Excellent raw snack for patients needing to increase vitamin C intake (e.g., for iron absorption).
Pumpkin/butternut squash	Beta-carotene: 3-5mg; Potassium: 230-350mg; Folate: 27µg; Manganese: 0.2mg	Widely available in Sudan and East Africa. Manganese is a cofactor for MnSOD (the mitochondrial antioxidant enzyme). Seeds are rich in zinc, magnesium, and phytosterols — do not discard.

WHY?

Fat-soluble vitamin absorption from orange vegetables is critically dependent on fat co-ingestion. Research shows that beta-carotene absorption from carrots or sweet potato eaten without fat is essentially negligible — the food matrix releases the carotenoids but they cannot be incorporated into chylomicrons for absorption without micellar fat. Adding 3-5g of fat (a teaspoon of oil, small amount of avocado, or a handful of nuts) to a carotenoid-rich meal increases absorption 2-10 fold. This is one of the most practical and actionable bioavailability principles in clinical nutrition.

Group 4 — Allium Vegetables

Garlic, Onions, Leeks, Shallots, Scallions — The Cardiovascular Vegetables

Allium vegetables are covered in depth in the Phytochemicals lecture (organosulfur compounds, allicin, quercetin). The key clinical points for practice are summarized here, with emphasis on the Sudanese dietary context.

Allium Vegetable	Key Nutrients Beyond Phytochemicals	Clinical Relevance
Garlic	Vitamin B6: 1.23mg/100g (70% RDA); Manganese: 1.67mg (87% DV); Vitamin C: 31mg; Selenium (soil-dependent); Fructooligosaccharides (FOS — prebiotic)	B6 for neurotransmitter synthesis and immune function; Mn for MnSOD; FOS feeds Bifidobacterium. Allicin (cardiovascular, antimicrobial) requires crushing then 10-min rest before heat. Meta-analysis (39 RCTs): reduces LDL, total cholesterol, TG, and SBP.
Onions	Quercetin (highest in outer layers, red > yellow > white); Fructans (prebiotic fibre); Chromium; Folate; Potassium	Quercetin: BP reduction, anti-inflammatory, anti-platelet. Fructans: prebiotic — feeds Bifidobacterium and Lactobacillus. Chromium: glucose tolerance factor — relevant in insulin resistance. Red onions highest in both quercetin and anthocyanins.
Leeks	Folate: 64µg/100g; Vitamin K: 47µg; Kaempferol (flavonol); Manganese	Kaempferol inversely associated with ovarian and lung cancer in epidemiological studies. Folate contribution meaningful if eaten regularly. The dark green tops contain more nutrients than the white bulb — encourage patients to use the whole vegetable.

CONTEXT

Garlic and onion are the flavour foundation of Sudanese, Egyptian, and East African cooking — present in virtually every savoury dish. This is nutritionally significant: patients eating traditional Sudanese cuisine are already receiving consistent doses of quercetin, allicin precursors, B6, manganese, and prebiotic FOS from their everyday cooking. The counselling message should be reinforcement and affirmation of this cultural practice — not replacement with unfamiliar foods.

Group 5 — Tomatoes, Peppers & Nightshades

Lycopene, Vitamin C, Capsaicin — From Raw to Cooked

Food	Key Nutrients	The Preparation Principle
Tomatoes (raw)	Lycopene: ~3mg/100g; Vitamin C: 14mg; Potassium: 237mg; Vitamin K: 7.9µg	Raw tomatoes have low lycopene bioavailability — lycopene is bound in chromoplasts. Vitamin C is preserved raw.

Tomatoes (cooked, especially with oil)	Lycopene: 9-17mg/100g (canned/cooked); higher cis-isomer proportion	Heat breaks cell walls and converts trans-lycopene → cis-lycopene (more bioavailable). Fat co-ingestion essential. Traditional tomato-based sauces cooked in olive oil are the optimal lycopene delivery system.
Tomato paste / concentrate	Lycopene: 45-55mg/100g (highest of any food)	The most potent lycopene source available. Even 1 tablespoon (30g) of tomato paste provides ~15mg lycopene. Clinical trials for prostate cancer chemoprevention used tomato products as the lycopene vehicle.
Red bell peppers	Vitamin C: 128mg/100g; Beta-carotene: 1.6mg; Capsanthin (carotenoid); Vitamin B6	Red peppers have 3x the vitamin C of oranges. Raw is best for vitamin C. Capsanthin contributes to provitamin A activity. Capsaicin in hot peppers: TRPV1 agonist — anti-inflammatory, analgesic, thermogenic.
Eggplant (aubergine)	Nasunin (anthocyanin in skin); Chlorogenic acid; Fibre: 3g/100g	Nasunin is a potent singlet oxygen quencher and iron chelator in the skin — do not peel. Chlorogenic acid inhibits glucose absorption. Low calorie density (25 kcal/100g) — excellent for weight management.

EVIDENCE

Lycopene and prostate cancer: Health Professionals Follow-up Study (n>47,000): Men in the highest vs lowest quintile of lycopene intake had a 35-40% lower risk of advanced prostate cancer (RR 0.60). Tomato product intake (sauce, paste, juice) inversely associated in 11 of 14 prospective studies reviewed. Lycopene 15mg/day pre-surgically in prostate cancer patients (Phase 2 RCT): reduced PSA, tumour proliferation index (Ki67), and oxidative DNA damage. The cooking-in-oil principle is mechanistically critical for achieving these lycopene doses from food.

Group 6 — Berries & High-Antioxidant Fruits

Blueberries, Strawberries, Pomegranate, Dates, Guava

Fruit (100g fresh)	Standout Nutrients	Key Health Evidence
Blueberries	Anthocyanins: 163mg; Vitamin C: 10mg; Vitamin K: 19µg; Manganese: 0.3mg; Resveratrol	CVD: 1 cup/day, 6 weeks → improved flow-mediated dilation in metabolic syndrome (RCT). Cognition: USDA/Tufts studies show reduced age-related cognitive decline. T2DM: improved insulin sensitivity. Anthocyanins cross blood-brain barrier.
Strawberries	Vitamin C: 59mg (79% adult RDA); Folate: 24µg; Fisetin; Anthocyanins; Ellagic acid	Vitamin C density; fisetin has senolytic activity (destroys senescent cells). Ellagic acid → urolithins (gut microbiome-dependent). CVD: ↓ LDL-C and CRP in RCTs.
Pomegranate	Ellagitannins (punicalagins): 300-400mg; Vitamin C: 10mg; Folate: 38µg; Potassium: 236mg	Urolithin production (gut-dependent); anti-inflammatory; 3-year RCT: ↓ carotid intima-media thickness (arterial plaque marker). Phase 2 trial: extended PSA doubling time in prostate cancer recurrence.
Dates	Potassium: 696mg; Magnesium: 54mg; Copper: 0.4mg; Iron: 1mg;	High nutrient density but very high sugar content — caution in T2DM; limit to 2-3 dates/day in

	Fibre: 7g; Natural sugars: ~67g/100g (dried)	glycaemic management. Potassium and magnesium content relevant for hypertension. Polyphenols (gallic acid, procyanidins) have antioxidant activity. Culturally important in Sudan and Middle East.
Guava	Vitamin C: 228mg (highest of any common fruit, ~3x RDA per 100g); Lycopene (pink varieties): 5.4mg; Potassium: 417mg; Folate: 49µg	Exceptional vitamin C source — one guava meets adult vitamin C requirement. Pink guava provides substantial lycopene. High fibre (5g/100g) slows glucose absorption. Widely available and affordable in Sudan and tropical Africa.
Kiwi	Vitamin C: 93mg; Vitamin K: 40µg; Folate: 25µg; Vitamin E: 1.5mg; Actinidin (protease)	One of the highest vitamin C densities among common fruits. Actinidin protease improves protein digestibility. RCT (n=54): 2 kiwis/day improved sleep quality and duration. Vitamin K relevant for bone health.

CONTEXT

Guava is one of the most nutrient-dense fruits available in Sudan and tropical Africa — providing more vitamin C per 100g than any citrus fruit, meaningful lycopene (pink varieties), potassium, and folate, at very low cost. Yet it rarely appears in nutrition counselling materials derived from Western food databases. Dates are nutritionally complex: high in potassium, magnesium, and polyphenols, but also very high in simple sugars — requiring nuanced counselling that respects their cultural significance while addressing glycaemic management.

Group 7 — Citrus Fruits

Oranges, Grapefruit, Lemons, Limes — Whole Fruit vs. Juice

Citrus fruits are historically significant as the first dietary cure for a major nutritional deficiency disease (scurvy). Beyond vitamin C, they provide folate, potassium, flavanones (hesperidin, naringenin), limonoids, and pectin (soluble fibre). The critical clinical distinction is whole fruit versus juice.

Comparison	Whole Citrus Fruit	Citrus Juice
Fibre	High (2-3g/fruit, including pectin)	Essentially zero — fibre is removed in juicing
Glycaemic impact	Low GI — fibre slows glucose absorption; gradual blood glucose rise	High GI — rapid glucose delivery without fibre; significant postprandial glucose spike
Flavanone bioavailability	Better — fibre slows gut transit → more time for colonic bacterial fermentation → more bioactive metabolites	Lower overall bioavailability despite higher initial absorption rate
T2DM risk	3 servings whole fruit/week (NHS data) → 26% ↓ T2DM risk	Fruit juice consumption associated with INCREASED T2DM risk in Nurses' Health Study I & II + HPFS combined (n>180,000)
Caloric density	Low — natural portion control from satiety	High in sugar per serving; easy to overconsume

Vitamin C	100% preserved if consumed soon after preparation	Degrades rapidly after pressing; 50% loss within 24 hours even refrigerated
Drug interaction (grapefruit)	Present but lower concentration of furanocoumarins	Most concentrated; single glass can cause clinically significant CYP3A4 inhibition persisting 24-72 hours

CAUTION

Grapefruit-drug interaction: Furanocoumarins in grapefruit irreversibly inhibit intestinal CYP3A4, dramatically increasing blood levels of CYP3A4-metabolised drugs. This is a genuine clinical safety issue. Affected drugs include: simvastatin/atorvastatin (rhabdomyolysis risk), cyclosporine (transplant rejection or toxicity), amlodipine (excessive BP drop), midazolam (excessive sedation), tacrolimus, amiodarone, and many others. One glass of grapefruit juice can affect drug metabolism for 24-72 hours. Patient education on this interaction is a core clinical dietitian responsibility.

Group 8 — Legumes

Lentils, Chickpeas, Fava Beans, Black-Eyed Peas, Soybeans

Although classified as protein foods in some dietary frameworks, legumes function nutritionally like a cross between vegetables and protein sources — providing exceptional micronutrient density alongside protein and fibre. They are a cornerstone of Mediterranean, DASH, and traditional Sudanese dietary patterns.

Legume (100g cooked)	Standout Micronutrients	Health Significance
Lentils	Folate: 181µg (45% RDA); Iron: 3.3mg; Zinc: 1.3mg; Potassium: 369mg; Thiamin: 0.17mg	Highest folate density of any common food; combined iron + folate ideal for IDA + megaloblastic anaemia prevention. Vitamin C co-ingestion triples iron absorption. Prebiotic fibre → Bifidobacterium. Ful (fava beans/lentils) is a Sudanese staple with exceptional nutritional value.
Chickpeas (hummus base)	Folate: 172µg; Zinc: 1.5mg; Manganese: 1.7mg (85% DV); Iron: 2.9mg; Magnesium: 48mg	Highest manganese content of common legumes; Mn is the cofactor for MnSOD. Chickpea peptides show ACE-inhibitory (antihypertensive) activity in RCTs. Resistant starch → SCFA production → colonocyte protection.
Fava beans (ful medames)	Iron: 2.5mg; Folate: 148µg; Potassium: 390mg; Zinc: 1.2mg; Protein: 7g	A traditional Sudanese and Egyptian staple with excellent micronutrient profile. Important note: fava beans can trigger haemolytic crisis in G6PD-deficient individuals — common in Sudan and East Africa. G6PD deficiency screening is relevant before recommending high fava bean intake.
Black-eyed peas (cowpeas)	Folate: 210µg; Iron: 2.5mg; Potassium: 278mg; Zinc: 1.3mg	Very high folate density. Widely consumed across Sub-Saharan Africa. Excellent base for folate counselling in women of reproductive age.

Soybeans / Edamame	Folate: 311µg; Iron: 2.3mg; Calcium: 102mg; Isoflavones: 40-60mg; Complete protein	Only plant food with all essential amino acids in adequate proportions. Isoflavone content relevant for menopausal symptom management (modest benefit in RCTs). Iron absorption enhanced by vitamin C co-ingestion.
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CAUTION

G6PD deficiency and fava beans: Glucose-6-phosphate dehydrogenase deficiency is an X-linked condition affecting approximately 10-20% of males in sub-Saharan Africa, Sudan, and the Middle East. Fava beans contain vicine and convicine, which produce hydrogen peroxide in G6PD-deficient red blood cells, causing acute haemolytic anaemia (favism). When counselling patients from these populations about increasing legume intake, it is important to be aware of this condition and to ask about any history of adverse reactions to fava beans before recommending them specifically.

PART THREE — The Cooking Question: How Preparation Affects What Patients Actually Receive

The same vegetable prepared by different methods can deliver dramatically different amounts of its key nutrients. Understanding this allows dietitians to give specific, actionable preparation guidance rather than simply telling patients to eat more vegetables.

Preparation Method	Vitamin C Retained	Folate Retained	Carotenoid Bioavailability	Glucosinolates/ Sulforaphane	Practical Guidance
Raw consumption	100%	100%	Low (cell walls intact)	Maximum (myrosinase active)	Best for vitamin C, folate, and sulforaphane. Not all vegetables are suitable raw — cruciferous, leafy greens, peppers are excellent raw. Carotenoid-rich vegetables (carrots, sweet potato) are better cooked + fat.
Steaming (5-10 min)	70-90%	~70%	Good (cell walls softened)	Good (myrosinase partly preserved)	Best all-around cooking method for most vegetables. Preserves water-soluble nutrients without leaching. Improves carotenoid release while protecting vitamins.
Boiling (high water volume)	30-50%	25-50%	Good but water-soluble compounds lost	Poor (myrosinase destroyed; glucosinolates leach into water)	Significant nutrient loss by leaching into water. If boiling, use minimal water, cook briefly, and retain cooking liquid for soups and sauces.
Microwaving	~90%	~80%	Good	Good (if brief)	Excellent vitamin C and folate retention due to short time and minimal water. Better than boiling for most nutrients.
Stir-frying with oil	~75%	~60%	Excellent (fat co-present)	Moderate	Fat co-ingestion significantly boosts carotenoid absorption. Brief time preserves vitamins.

					Preferred method for leafy greens and carotenoid-rich vegetables.
Roasting / Baking	~40%	~50%	Good (fat usually present)	Moderate	Concentrates minerals and fibre. High AGE formation but reduced anti-nutrients. Good for root vegetables; not ideal for vitamin C-rich vegetables.
Fermenting	Variable (some synthesis)	Variable (microbial synthesis may increase)	Variable	Variable	Reduces phytate (improves mineral bioavailability); produces probiotics and SCFAs; isoflavone deglycosylation improves absorption. Traditional fermented foods (Sudanese kiswa fermented sorghum flatbread, yogurt) support gut microbiome.
Freezing (after blanching)	70-80% (stable thereafter)	~60-70% (stable thereafter)	Comparable to fresh-cooked	Reduced	Frozen vegetables are nutritionally equivalent or superior to fresh stored for several days. Blanching before freezing destroys some nutrients but stabilizes the rest. Counsel food-insecure patients that frozen is an excellent choice.

PRACTICE

The most important preparation rules for practice: (1) Steam cruciferous and leafy green vegetables rather than boil. (2) Cook tomatoes with oil for maximum lycopene. (3) Eat raw bell peppers, leafy greens, and citrus for maximum vitamin C. (4) Add fat (oil, avocado, nuts) to salads and carotenoid-rich vegetable dishes. (5) Chop garlic and allow 10 minutes before cooking. (6) If boiling is the only method available, use minimal water and retain the cooking liquid. (7) Frozen = fresh nutritionally — use this to overcome the cost and availability barrier.

Storage and the 'Fresh vs. Frozen' Question

A widespread misconception is that fresh vegetables are always nutritionally superior to frozen. The evidence does not support this. Fresh vegetables stored for 3-5 days at room temperature or in the refrigerator lose substantial amounts of heat-labile and oxidation-sensitive nutrients:

- Spinach loses approximately 50% of its folate within 4 days of refrigerator storage.
- Broccoli loses approximately 56% of its vitamin C within 5 days of storage.
- Frozen vegetables are blanched (brief hot water treatment) then immediately frozen — the blanching causes some initial loss but then preserves the remaining nutrients for months.
- Studies comparing frozen vs. fresh vegetables stored for 5+ days consistently show comparable or superior nutrient content in frozen produce for vitamin C, folate, and beta-carotene.
- The practical implication: for patients with limited access to fresh produce, or who waste fresh produce, frozen vegetables are a nutritionally equivalent and economically superior option.

PART FOUR — How F&V Protect Against Specific Diseases

The disease-protective effects of F&V work through multiple simultaneous mechanisms, which is why whole food consumption is more protective than isolated nutrients or supplements. The three diseases with the strongest evidence for F&V protection are examined here.

Cardiovascular Disease

From Potassium to Polyphenols — Multiple Protective Mechanisms

Mechanism	F&V Components Involved	Clinical Evidence
Blood pressure reduction via potassium	Potassium from bananas, sweet potato, leafy greens, legumes, tomatoes. Potassium promotes renal sodium excretion and reduces vascular tone.	DASH diet (8-10 servings F&V/day): -3 to -6 mmHg SBP beyond control diet. Effect comparable to single antihypertensive medication in mildly hypertensive patients. Potassium intake $\leq 4,700$ mg/day (DASH level) vs average $\sim 2,600$ mg/day in most populations.
LDL cholesterol reduction via soluble fibre	Pectin (citrus, apples), beta-glucan (oats), mucilage (okra), guar gum (legumes). Soluble fibre binds bile acids in the gut $\rightarrow$ excreted rather than recycled $\rightarrow$ liver draws on cholesterol to make new bile acids.	Meta-analyses: 3-5g/day soluble fibre $\rightarrow$ 5-10% LDL-C reduction. FDA-approved health claim for soluble fibre and reduced CHD risk. Okra mucilage and legume fibre are particularly relevant sources in Sudanese dietary context.
Antioxidant protection of LDL from oxidation	Vitamin C (citrus, peppers, kale), vitamin E (leafy greens, avocado), carotenoids (carrots, sweet potato, tomatoes), polyphenols (berries, onions, garlic).	Normal LDL is not directly atherogenic; oxidized LDL (oxLDL) is. Mediterranean diet (PREDIMED, n=7447): 30% $\downarrow$ major CVD events, associated with lower oxLDL and F2-isoprostane levels. F&V polyphenols reduce LDL oxidation in multiple RCTs.
Endothelial function improvement	Anthocyanins (berries), flavanols (cocoa, tea), nitrate (leafy greens converted to NO in the body), lycopene (tomatoes).	Blueberry RCTs: 1 cup/day, 6 weeks $\rightarrow$ significant improvement in flow-mediated dilation (FMD — the measure of endothelial function). Green leafy vegetable intake inversely associated with CVD mortality in EPIC and NHS cohorts — partly via nitrate $\rightarrow$ nitric oxide pathway.
Anti-inflammatory effects	Quercetin (onions, kale), anthocyanins (berries), sulforaphane (cruciferous), omega-3 precursors (flaxseed ALA).	hsCRP (inflammation marker) is inversely associated with F&V intake in large cohort studies. DASH and Mediterranean dietary patterns consistently reduce hsCRP — the anti-inflammatory mechanism partly explains their CVD protection beyond lipid effects.

EVIDENCE

The most robust epidemiological evidence: Aune et al. (Int J Epidemiol 2017, 95 prospective cohort studies, n>2.5 million): ≥ 5 servings F&V/day vs < 1 serving $\rightarrow$ HR 0.80 for CVD mortality, 0.74 for ischaemic heart disease, 0.81 for stroke. The DASH diet — which emphasizes 8-10 daily F&V servings — reduces blood pressure by 3-6 mmHg SBP and 2-3 mmHg DBP beyond a control diet, an effect size comparable to antihypertensive medication in mild hypertension.

Cancer

Specific Vegetables for Specific Cancers — Evidence-Based Targeting

Cancer Type	F&V with Strongest Evidence	Mechanism	Evidence Grade
Prostate cancer	Tomatoes/lycopene (cooked with fat); cruciferous vegetables	Lycopene: singlet O ₂ quenching in prostate tissue; inhibits IGF-1; Nrf2 activation. Sulforaphane: Phase II enzyme induction; HDAC inhibition; inhibits cancer cell proliferation.	STRONG epidemiological (40% risk reduction in high lycopene consumers); Phase 2 RCT data for sulforaphane.
Colorectal cancer	Cruciferous vegetables; allium vegetables; fibre-rich legumes and whole F&V	Sulforaphane and DIM: Phase II enzymes; HDAC inhibition; apoptosis induction. Fibre: dilutes carcinogens; reduces transit time; promotes SCFA production (butyrate protects colonocytes). Quercetin: anti-proliferative.	STRONG epidemiological; WCRF probable protective evidence for non-starchy vegetables and fibre.
Gastric cancer	Allium vegetables (garlic, onions) — most specific evidence	Allicin and organosulfur compounds: anti-H. pylori activity; pro-apoptotic in gastric cancer cells. 6-fold higher gastric cancer rates in populations with low allium consumption.	STRONG epidemiological; allium-gastric cancer association among the most consistent in cancer nutrition literature.
Lung cancer (non-smoker)	Cruciferous vegetables; beta-carotene-rich fruits and vegetables	Sulforaphane/PEITC: inhibit carcinogen-activating CYP enzymes (CYP2E1, CYP2A6); Phase 2 trial: watercress meal reduced tobacco carcinogen metabolites in smokers. Beta-carotene from food (not supplements) inversely associated with lung cancer.	MODERATE epidemiological; mechanistic Phase 2 trial data. IMPORTANT: high-dose beta-carotene SUPPLEMENTS increase lung cancer in smokers — food sources are safe.
Breast cancer (postmenopausal)	Cruciferous vegetables; flaxseed lignans; soy isoflavones (Asian cohort data)	DIM: modifies oestrogen metabolism to less active forms. Enterolactone (from flaxseed lignans): weak oestrogenic activity — may compete with oestrogen at receptors. Equol (from soy): depends on gut microbiome capacity.	MODERATE; lignan and isoflavone associations consistent in prospective cohorts; WCRF: moderate evidence for cruciferous vegetables.

CAUTION

Important clinical caution on antioxidant supplements during cancer treatment: While F&V intake before and after cancer treatment is consistently protective, high-dose antioxidant supplement use during active chemotherapy or radiotherapy may reduce treatment efficacy. Chemo and radiotherapy work partly by generating free radicals that kill cancer cells. High-dose antioxidants may protect tumour cells as well as normal tissue. Counsel cancer patients to maximise whole food F&V intake, but to discuss antioxidant supplement use with their oncologist before starting during treatment.

Type 2 Diabetes — Non-Starchy Vegetables and the Whole Fruit Rule

The Evidence Behind Two of the Most Important T2DM Counselling Principles

F&V Category	Effect on T2DM Risk or Management	Key Evidence
Non-starchy vegetables (all types)	Lowest glycaemic impact of any food group; universally safe in T2DM; form the dietary foundation of the ADA Diabetes Plate Method	ADA Standards of Care: non-starchy vegetables should fill half the plate at every meal. No upper limit in T2DM management. Magnesium and potassium from leafy greens improve insulin sensitivity independently of carbohydrate effects.
Whole fruit (NOT juice)	3 servings/week of whole fruit → 26% ↓ T2DM risk. Effect strongest for blueberries, grapes, apples, pears.	NHS I & II + HPFS combined (n>180,000): Whole fruit protective, fruit juice associated with INCREASED risk. Restricting all fruit in T2DM is NOT evidence-based and deprives patients of important micronutrients, fibre, and phytochemicals.
Dark leafy greens specifically	1.35 additional servings/day → 14% ↓ T2DM risk	Meta-analysis of 6 prospective studies. Contributing mechanisms: magnesium (insulin receptor function), alpha-lipoic acid, folate, polyphenols, low glycaemic load.
Cruciferous vegetables	Inverse association in EPIC and NHS cohorts; broccoli sprout extract (RCT, n=81 T2DM patients): significant ↓ fasting glucose and HbA1c vs placebo at 12 weeks	Sulforaphane reduces hepatic glucose output and improves insulin sensitivity in cell and animal models. Human RCT data now confirms mechanistic predictions.
Legumes	Consistently associated with improved glycaemic control and T2DM prevention in cohort data. GI of legumes is 30-40 vs 70-90 for white bread.	Viscous fibre (pectin, guar gum) slows carbohydrate absorption; resistant starch bypasses small intestine; phaseolamin (in beans) inhibits alpha-amylase. A meal with legumes reduces postprandial glucose by 30-50% compared to an equivalent starch meal.
High GI fruits (caution)	Watermelon (GI~76), overripe banana (GI~62), pineapple (GI~59) — can cause significant postprandial glucose rises in T2DM	In active glycaemic management: prefer low GI fruits (berries GI~25-40, apples GI~36, citrus GI~40-50). Portion size matters: a small banana (80g) has less glycaemic impact than a large one (200g).

PRACTICE

The whole fruit versus juice principle deserves emphasis in every T2DM consultation. Many patients with T2DM believe they must eliminate all fruit — this is incorrect and deprives them of important nutrients. The evidence shows that 2-3 servings of whole low-GI fruit daily is safe and beneficial in T2DM. What must be limited is fruit juice, which delivers sugar without fibre and causes rapid glycaemic excursions. Reinforce: whole fruit ✓, fruit juice ✗ for glycaemic management.

PART FIVE — Counselling in Practice: Overcoming the Real Barriers

Understanding the nutrition science of F&V is necessary but not sufficient for clinical practice. The gap between knowledge and intake is large — even patients who know vegetables are good for them often fail to eat adequate amounts. Effective counselling requires understanding and addressing the actual barriers patients face.

Barrier	How It Manifests	Evidence-Based Strategy
Cost	Fresh produce is expensive relative to calorie content; F&V cost more per calorie than ultra-processed alternatives in most markets	Frozen = fresh nutritionally at lower cost. Seasonal F&V are 30-50% cheaper. Legumes are the most nutrient-dense affordable F&V-equivalent. Growing herbs and small vegetables at home (mint, tomatoes, spring onions) is accessible even in small spaces.
Time and preparation	Patients believe fresh vegetables require too much preparation time	Pre-washed, pre-cut, or frozen vegetables require no preparation. One-pot vegetable soups and stews are fast. Teaching simple 15-minute vegetable-heavy meals increases sustained intake more than complex recipes.
Spoilage and waste	Fresh produce spoils quickly; patients with inconsistent shopping routines waste money	Frozen vegetables have no spoilage. Buying smaller amounts of fresh produce more frequently, or buying varieties that keep longer (carrots, cabbage, sweet potato, onions, garlic) reduces waste.
Unfamiliarity and taste preference	Patients may not know how to prepare certain vegetables; children and adults raised on low-vegetable diets may find vegetables unpalatable	Build recommendations around vegetables the patient already eats. Offer preparation methods that improve palatability (roasting, adding spices and herbs). Gradual introduction is more sustainable than radical dietary change.
Cultural disconnect	Standard nutrition materials recommend unfamiliar vegetables (Brussels sprouts, kale) while ignoring culturally central ones (molokhia, okra, fenugreek, bitter melon)	Identify and affirm the nutritional value of culturally familiar F&V before recommending new ones. Translate the nutrient content of traditional dishes into the counselling framework. For Sudanese patients: molokhia, bamia (okra), ful, lentils, garlic, onions are nutritionally excellent — say so explicitly.
Misconceptions	'Fruit is full of sugar'; 'frozen is not as good as fresh'; 'cooking destroys all the nutrients'; 'supplements are better than vegetables'	Each of these misconceptions requires specific targeted education. The evidence is clear: whole fruit is safe and beneficial (even in T2DM); frozen is nutritionally equivalent to fresh; some cooking methods improve bioavailability; supplements do not replicate whole food benefits.
Access	In food-insecure settings, fresh produce is not consistently available	Validate the structural barrier; focus on affordable, shelf-stable F&V equivalents (dried legumes, canned tomatoes, frozen vegetables, root vegetables, dried fruits in moderation). Connect with social support resources where available.

The Colour Framework — A Simple, Actionable Counselling Tool

The 'eat the rainbow' principle is more than a slogan — different pigments in F&V reflect different phytochemical families with different protective mechanisms. Aiming for variety across colour categories is a simple, memorable goal that patients can track and that correlates with phytochemical diversity.

Colour	Primary Phytochemicals	Priority F&V Sources	Why These Colours Matter
RED	Lycopene, anthocyanins, ellagic acid	Tomatoes (especially cooked), watermelon, strawberries, cherries, red peppers, pomegranate, red cabbage	Lycopene: prostate and cardiovascular protection. Anthocyanins: endothelial function, neuroprotection. Ellagic acid: urolithins via gut microbiome.
ORANGE / YELLOW	Beta-carotene, alpha-carotene, vitamin C, hesperidin	Sweet potato, carrots, pumpkin, orange/yellow peppers, oranges, mango, papaya, guava	Provitamin A (beta-carotene): vitamin A deficiency prevention. Vitamin C: immune function, iron absorption. Hesperidin: anti-inflammatory, lipid-lowering.
GREEN	Sulforaphane, lutein/zeaxanthin, folate, vitamin K, vitamin C, chlorophyll	Broccoli, spinach, kale, Brussels sprouts, molokhia, bok choy, edamame, avocado, kiwi, green tea, bamia	Sulforaphane: most potent dietary Nrf2 activator. Lutein/zeaxanthin: macular protection. Folate: one-carbon metabolism, NTD prevention. Vitamin K: bone and vascular health.
BLUE / PURPLE	Anthocyanins, resveratrol, pterostilbene	Blueberries, blackberries, purple grapes, eggplant, purple cabbage, red onion (outer skin), beet, plum	Anthocyanins: cross blood-brain barrier; neuroprotective; strongest endothelial function evidence. Resveratrol: SIRT1/mitochondrial health.
WHITE / BROWN	Allicin, quercetin, kaempferol, inulin (prebiotic)	Garlic, onions, leeks, cauliflower, mushrooms, white asparagus, dates, chickpeas	Allicin: antimicrobial, cardiovascular. Quercetin: BP reduction, anti-inflammatory. Inulin/FOS: prebiotic, gut microbiome support.

PRACTICE

Use the colour goal in counselling: Ask the patient to aim for at least 3 different colour categories daily. This is more actionable than specifying grams or cup quantities, and correlates with dietary diversity. A simple phone photo log or tally card works well as a self-monitoring tool. Research shows that colour diversity of F&V intake correlates with phytochemical diversity and with health outcomes in prospective studies.

Special Population Considerations

Pregnant and Lactating Women

- Folate priority: ≥ 400 -800 μ g/day periconceptionally. Dark leafy greens (molokhia, spinach), legumes (lentils, black-eyed peas), and citrus are the best dietary folate sources. Supplement is still required alongside dietary sources.
- Iron: Combine iron-rich plants (lentils, dark greens) with vitamin C sources (guava, orange, red pepper, tomato) at every meal. Non-haem iron absorption increases 2-3 fold with vitamin C co-ingestion.
- Vitamin A: Beta-carotene from sweet potato, carrots, and leafy greens safely meets needs. Preformed retinol from animal sources can be teratogenic at very high doses — plant-based provitamin A is the safer source during pregnancy.
- Food safety: Avoid raw sprouts (*Listeria*, *Salmonella* risk); wash all F&V thoroughly; choose pasteurized juices over fresh-squeezed.

Older Adults (≥ 65 years)

- Reduced gastric acid production $\rightarrow$ impaired B12, Fe, Ca, and Zn absorption from many foods. F&V provide easily absorbed alternatives: plant calcium from low-oxalate sources (bok choy, kale, broccoli), vitamin C to enhance non-haem iron absorption.
- Sarcopenia risk: Protein intake per meal is critical; combine F&V with protein-rich foods (legumes, eggs, dairy, fish) rather than vegetable-only meals.
- Dysphagia or dental issues: Soft-cooked and pureed vegetables; blended soups; smoothies incorporating leafy greens; cooked fruit compotes.
- Polypharmacy: Warfarin (consistent vitamin K intake from leafy greens); grapefruit (CYP3A4 interactions with statins, cyclosporine, amlodipine).

Vegans and Strict Vegetarians

- Calcium: Use low-oxalate sources (bok choy, kale, broccoli, fortified plant milks) — not spinach. Target $\geq 1,000$ mg/day from food.
- Iron: Combine legumes and dark greens with vitamin C at every meal. Cooking in cast iron increases non-haem iron content of food slightly. Avoid tea and coffee with meals (tannins inhibit iron absorption).
- Zinc: Legumes, seeds (pumpkin seeds especially), and whole grains. Soaking and fermenting legumes reduces phytate and improves zinc bioavailability.
- Vitamin B12: NOT found in any F&V. Supplementation is non-negotiable for strict vegans — regardless of how nutritious their plant-based diet is otherwise.
- Omega-3: Flaxseed, chia, and walnuts provide ALA, but conversion to EPA/DHA is inefficient. Algal DHA supplement recommended.

Patients with CVD or Hypertension

- DASH diet implementation: Target 8-10 servings F&V daily. Emphasise potassium-rich sources: sweet potato (475mg/100g), bananas (358mg), leafy greens, legumes, tomatoes.
- Sodium management: Canned vegetables may contain added sodium — choose no-added-salt versions or drain and rinse (removes $\sim 40\%$ of sodium).

- Potassium caution in advanced CKD (eGFR<30): Restrict high-K F&V; leaching (boiling and discarding the water) reduces potassium content by ~50%, allowing safer vegetable inclusion even in dialysis patients.

Patients with Type 2 Diabetes

- Non-starchy vegetables: unlimited — they form the foundation of the Diabetes Plate Method (half the plate).
- Whole fruit: 2-3 servings/day of low-GI fruits (berries, apples, citrus, guava) is safe and beneficial. Restrict juice.
- Starchy vegetables (sweet potato, corn, peas): count toward carbohydrate budget, but have lower GI than refined grains and provide much higher micronutrient density.
- Glycaemic pairing: Combining F&V with protein and fat at meals further reduces postprandial glucose excursions.

Clinical Scenario: Putting It All Together: Nadia, 38 Years Old, Port Sudan

- Nadia is a 38-year-old teacher in Port Sudan. She has been recently diagnosed with hypertension (145/92 mmHg), her fasting glucose is 6.2 mmol/L (pre-diabetes), and she has mild iron deficiency anaemia (Hb 10.8 g/dL, ferritin 8 ng/mL). She is 3 months postpartum and breastfeeding. Her diet consists primarily of white rice, flatbread, some meat 3-4 days/week, and tea with every meal. She eats garlic and onion daily in cooking. She occasionally eats fruit (mango, watermelon when in season). She rarely eats vegetables separately from cooking. She says she does not have time to prepare 'special' foods.
- Question 1: Using the clinical reasoning from this lecture, identify the 5 most important F&V counselling priorities for Nadia, ranked by clinical urgency. For each, specify the food, the mechanism, and the preparation guidance.
- Question 2: Nadia says she already uses garlic and onions in all her cooking, tomatoes in most dishes, and sometimes molokhia. What nutritional value is she already receiving from these? How would you acknowledge and build on this?
- Question 3: She is concerned about the cost of adding more vegetables to her diet. Which affordable, accessible F&V would you prioritize for her situation in Port Sudan? (Consider what is locally available and seasonally accessible in Sudan's Red Sea State.)
- Question 4: She drinks 4-5 cups of tea per day with her meals. What specific counselling would you give about timing of tea consumption relative to her iron-containing foods?
- Question 5: She asks whether she should take a 'vitamin and mineral supplement' instead of changing her diet, as it is easier. How would you respond, using the evidence from this lecture series?

Critical Thinking Questions

- This lecture describes molokhia, bamia (okra), ful medames, guava, and dates as nutritionally important but largely absent from Western nutrition textbooks and dietary guidelines. What are the implications of this gap for how we train dietitians and design nutritional counselling tools? How might a dietitian working in Sudan or East Africa adapt evidence-based recommendations developed primarily in Western research contexts?

- The evidence consistently shows that frozen vegetables are nutritionally equivalent to fresh stored produce, yet many patients (and some health professionals) perceive fresh as inherently superior. How would you address this misconception with a patient who is food-insecure and cannot afford fresh produce consistently? What language would you use?
- The G6PD-fava bean risk described in this lecture is an example of a pharmacogenomic food interaction that is highly population-specific. What does this tell us about the limits of universal dietary recommendations? How should clinical dietitians approach population-specific food risks that may not be covered in their training?

Lecture Summary — Key Takeaways for Dietetic Practice

- F&V are nutritionally irreplaceable: they are the primary dietary sources of vitamin K1, folate, vitamin C, lutein/zeaxanthin, lycopene, and most dietary phytochemicals. Insufficient intake causes ~7.8 million preventable deaths/year globally. No supplement replicates the food matrix benefit.
- Group-by-group clinical priorities: Dark leafy greens (K1, folate, lutein, Mg, Ca, Fe); Cruciferous (C, K1, sulforaphane — steam, don't boil); Orange/yellow (beta-carotene — cook with fat); Alliums (quercetin, allicin — crush garlic before cooking); Tomatoes/nightshades (lycopene — cook with oil); Berries/high-antioxidant fruit (anthocyanins, ellagitannins, vitamin C); Citrus (whole fruit, not juice); Legumes (folate, iron, zinc, fibre, phytochemicals — essential for plant-based diets).
- Preparation matters critically: Steam > microwave > stir-fry > boil for vitamin C, folate, and sulforaphane. Cook tomatoes with oil for lycopene. Crush garlic before heating. Add fat to carotenoid-rich dishes. Frozen = fresh nutritionally. Boiling water can be retained for soups to recover leached water-soluble nutrients.
- Disease connections: CVD (potassium for BP; soluble fibre for LDL; antioxidants for LDL oxidation; polyphenols for endothelial function). Cancer (lycopene: prostate; sulforaphane: multiple; allium organosulfur: gastric; fibre: colorectal). T2DM (non-starchy vegetables: unlimited; whole fruit, not juice, reduces T2DM risk; cruciferous extract reduces HbA1c in RCT).
- Critical counselling principles: Whole fruit ✓ — fruit juice ✗ for glycaemic management. Frozen = fresh nutritionally — use to address cost barriers. Warfarin: consistent K1 intake, not avoidance. Grapefruit: CYP3A4 drug interaction risk (statins, cyclosporine, amlodipine). G6PD deficiency: caution with fava beans in at-risk populations (common in Sudan and East Africa).
- Cultural competency is non-negotiable: Molokhia, bamia, ful medames, guava, dates, and traditional garlic/onion-heavy cooking practices are nutritionally excellent. Effective counselling in Sudan and similar contexts reinforces the value of traditional F&V before recommending unfamiliar ones. The goal is dietary improvement within a culturally meaningful framework — not dietary replacement.

Suggested reading:

1. Aune D et al. (2017). Fruit and vegetable intake and the risk of CVD, total cancer, and all-cause mortality. *International Journal of Epidemiology*. |
2. WCRF/AICR Third Expert Report (2018). Diet, Nutrition, Physical Activity and Cancer: A Global Perspective. |
3. US Dietary Guidelines for Americans 2020-2025. |
4. Fung TT et al. (2009). Whole-grain intake and the risk of type 2 diabetes: a prospective study. *Am J Clin Nutr*. |
5. Blumberg JB et al. (2022). Impact of Frequency of Multi-Vitamin/Multi-Mineral Supplement Intake on Nutritional Adequacy. *Nutrients*.